ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 22 (O.S., Vol. XXVII) MAY, 1945 NUMBER 5

CONTENTS

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1938.

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VOLUME 22 MAY, 1945 NUMBER 5

HEART DISEASE IN THE JUNGLES OF THE SOUTH PACIFIC: SOME OBSERVATIONS MADE AMONG THE MELANESIANS OF THE NEW HEBRIDES AND SOLOMONS ISLANDS AREA *

By ALBERT SALISBURY HYMAN, F.A.C.P., Commander (MC), USNR

PREFACE

IN the spring of 1942 a new page was written into the history of United States naval warfare; the technic of "island hopping" was being developed in the South Pacific theatre of the war. As island after island of the New Hebrides and Solomons groups was wrested from enemy control, the plan of occupation called for perfect timing and teamwork between marine combat fighting units, naval construction battalions, and the task force land based staff which included the medical, communications, and supply stations. From out of wild jungle terrain there were hacked almost over night temporary landing strips and huge air fields for the fighting and supply planes. The change from the isolated solitude of some of the most primitive spots in the world to the tumultuous traffic of a busy international airport occurred in an unbelievably short time.

Although mechanized equipment played a great rôle in the building of these tremendous projects, manual labor was needed to complete many tasks. It became necessary to supplement the regular naval personnel with laborers selected from the native Melanesian population of the islands. An experiment with an initial group of about 45 youths and men drawn from various tribes and settlements showed them to be cheerful and willing workers with a remarkable ability to learn by imitation; by carefully watching the actions of the instructor, it required but little time and patience for most of the natives to become adept with the pick and shovel, hammer and saw, and even with some mechanical tools.

* Received for publication January 6, 1945.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

The success of this native labor venture led to the development of a larger plan to establish complete battalions of Melanesians from the various islands of the New Hebrides and Solomons groups. A special recruiting unit was set up to visit the more thickly populated areas in order to select the candidates for this native labor battalion. This unit consisted of naval officers from construction battalions, interpreters, medical officers, corpsmen, and a few French colonists who were familiar with the islands situation. It was my good fortune to have been the Senior Medical Officer of the party.

Experience soon taught that the value of any given native in such a labor battalion was in direct proportion to his health and his freedom from the multitude of tropical diseases prevalent throughout this area of the South Pacific. Malaria, amebic dysentery, dengue, hookworm, yaws, tsutsugamushi fever, filariasis, and the fungus infections are but a few of the more common disabling conditions which were found among the Melanesians of nearly every island. For this reason, every candidate was given a more or less complete physical examination before he was subjected to other tests to determine his desirability as a member of the labor unit; many could be screened out on mere inspection whereas others were again carefully examined before they were finally admitted to the native compound near the work project.

Although the recruiting party was primarily interested only in young able bodied men, it soon became evident that much good will was engendered by paying some medical attention to women and children, and it was not long before whole settlements would turn out for examination whenever we arrived at a new location. An opportunity was thus given to see several hundred natives, some from extremely primitive groups not far removed from the headhunters of Malakula and other savage islands.

While the natives presented many other medical problems, I was especially interested in the various cardiovascular diseases which were discovered; for here I had an opportunity of investigating the development of certain heart and blood vessel conditions free from the so-called pernicious rôle of modern civilization with its continuous emotional stress, highly refined foods, lack of exercise, alcohol, tobacco, drugs, and the host of other alleged evils. If the current belief that the high incidence of heart disease is the result of a way of living, then these Melanesians in their jungle paradise should be relatively immune to such conditions as high blood pressure, arteriosclerosis, coronary heart disease, and peripheral vascular disturbances.

Arteriosclerosis

One of the most striking early observations about these people of the jungle is the general absence of very old individuals with gray hair; the explanation was simple. Longevity is not the rule in the jungle, either among men or beasts. The oldest persons seen were among the women; calculated from the native scheme of determining time (lunar calendar),

they were about 55 to 58 years old. The oldest men were said to be about 50. After the age of 18 most individuals appeared to be from 10 to 20 years older than their actual age.

The incidence of obvious arteriosclerosis was high in those of 30 and older; prominent and tortuous temporal arteries was a common sight in nearly all of these. The radial arteries were thickened and rigid and the dorsalis pedis was difficult to palpate in many. The beaded type of calcification was less common than the generalized, but some of the older women showed the Pal-Winterberg form of arterial sclerosis. Oriental cataract is frequent and the natives readily permitted fundus examination, but they did not take kindly to nose and throat or ear investigation. Changes in the retinal vessels appeared early in life; some were rather extreme.

One gained the impression that vascular degenerative pathologic lesions started earlier in these Melanesians than in comparative groups of Americans or Europeans; this was particularly true of the peripheral vascular disturbances. I shall have occasion to speak more fully of this at a later time.

Blood Pressure

In general, no objection was made to the taking of blood pressure; the natives wear several ornamental arm bands which frequently are so tight that there is considerable edema below the constricting rings. Inflation of the blood pressure cuff never failed to cause them amusement and they were fascinated by the movements of the manometer needle. There were some differences in the pressures of individual groups on the various islands; a certain large settlement was found to have a number of persons with rather low levels: 80–90 mm. Hg systolic and 40–50 mm. diastolic. On other islands the blood pressure levels were more or less similar to those of Americans of equal age, weight, and sex.

Of no little interest, however, were the findings on three islands which were some distance from each other. A group of individuals, both men and women, had rather high systolic blood pressure levels: 180–235 mm. Hg systolic to 96–115 mm. diastolic. In one tribe which consisted of a much inter-married family, 11 persons out of 19 over the age of 30 who were examined had elevated systolic pressures. In this same settlement a boy of about 18 had a blood pressure of 160 mm. Hg systolic and 104 mm. diastolic. These groups of hypertension were worthy of far more study and attention than it was possible to give; the non-medical members of the recruiting party were naturally interested only in healthy natives and any time devoted to those who could not meet the required physical standards was considered in a good natured way as holding up the war effort. Thus only a most cursory examination of these hypertensive cases was possible.

Outside of the factor of consanguinity, there did not appear any other reason for the higher blood pressure levels in these Melanesians than in their neighbors on nearby islands. The problems of food, climate, exposure to

tropical infestation, and environment are about the same on all of the islands visited. Why, then, the hypertensive syndrome in these few isolated settlements? A provocative suggestion came from one of the French colonial plantation owners who had lived in this part of the tropics for more than 30 years and who seemed to have a veritable storehouse of information concerning the South Pacific. He said that there was a current belief among the Native Practitioners that black water fever was frequently followed by hypertension. He was patient enough to question at some length, in the various dialects of pidgin English, nine of the Melanesians who had high blood pressure and found in six a more or less definite history of hematuria or the passing of very dark colored urine during an especially severe episode of chills and fever which had been treated with quinine.

Black water fever was not a common complication among the combat personnel during the early days of the Solomons campaign; I have previously reported [1] that from October 1942 up to May 1943 several thousand cases of malaria were seen at a certain advanced base hospital with a very small incidence of the condition. The follow-up of some of these cases has not shown any permanent renal damage. The available literature upon black water fever does not mention hypertension as a possible sequela to the condition and there is but vague reference to late kidney disease in these cases. This is still one of the great unexplored problems associated with malaria control but I have the unproved impression that certain tropical diseases may be productive of hypertension as the secondary result of renal damage.

Another interesting side light was obtained in regard to the incidence of high blood pressure among these Melanesians; pre-eclamptic toxemia is apparently not unknown. I was told that in a prominent tribal family nearly all of the women had experienced this difficulty and that there had been two deaths.

The end result of long standing hypertension was seen in two individuals who had suffered hemiplegia; the interpreters said that apoplexy was known to the natives who have a special word for one-sided paralysis: *nomuffaf* which may be the contraction of "no move half." Pidgin English has many such contractions of two or more words.

Cardiac Hypertrophy

We were all impressed by the number of hearts which seemed to be enlarged by simple percussion and inspection; roentgen-ray was not available in the field but several natives were subsequently examined at the advanced base hospital and they all had a general cardiac hypertrophy without any other signs of heart disease. Eleven men were accepted in the labor unit all of whom had evidence of enlarged heart; the apex impulse was in the sixth interspace and outside of the midclavicular line but they presented no other clinical indications of cardiovascular impairment. Reëxamination

several months later after they had completed their work and were being returned to their home islands showed no change.

Irregularities of the Heart

Tachycardia with rates as high as 160 was not uncommon during the first examination of these men; later the rates were easily controlled by vagal respiratory tests. The native Melanesians apparently have a very labile and responsive autonomic system; the exercise test was usually exaggerated but much of this was psychosomatic. When they became accustomed to the company of the Americans and to the medical personnel, all of their reactions became less violent and more controlled but some continued to have accelerated pulse rates during the several months that they were under observation. I saw no evidence of hyperthyroid disease and goiter is unknown.

An *extrasystolic arrhythmia* was discovered in a few individuals, both men and women; these premature contractions also appeared to be chiefly psychosomatic, but some of the natives said that they had experienced heart consciousness for a long period of time. This was described in a variety of ways, but the hand was invariably placed over the precordium as they discussed the matter with the interpreter.

Only one case of *auricular fibrillation* was discovered, but the Chief Native Practitioner said that he had seen several; he spoke of *delirium cordis* and said that it occasionally occurred during the course of some of these severe tropical fevers. He had also seen a number of cases of *paroxysmal tachycardia*. These had been chiefly among the women and especially during their climacteric; no explanation was given in regard to this unusual occurrence of the condition. There apparently had been no disastrous results and they all had gotten well.

Murmurs

A great number of murmurs were heard; these were largely *systolic* in time and were more or less localized over the pulmonic valvular area. They had the characteristics of so-called functional pulmonic systolic murmurs and were not associated with any other obvious cardiovascular disease. This murmur appeared in equal frequency in all age groups examined and in many thin individuals the murmur was loud enough to be evaluated as grade 2 or 3. The possibility of some vague tropical infection of the pulmonic valve or artery was considered but there was no evidence of other signs and symptoms associated with syndromes like Ayerza's disease.

Apical systolic murmurs were also quite frequent; these showed the usual changes in quality and duration depending upon posture, exercise, and breath holding. They were all classified as functional and were not associated with any other signs of heart disease; in a few men with hyper-

trophied hearts, however, this murmur was regarded with some suspicion but there was no proof that the combination was not purely coincidental.

Aortic diastolic murmurs were the most common of the group considered to be pathologic; these cases were discussed at some length with the Native Practitioners. Several investigations have been made at the Fiji Medical School and at the Royal French Hospital at Noumea, New Caledonia concerning the syphilis-like infections occurring in the South Pacific jungles. Yaws, tropical leprosy, and chronic tsutsugamushi disease are but a few of the various conditions which simulate syphilis in certain pathologic processes. In addition, several tropical fevers like malaria, dengue, and sand fly fever frequently cause positive Kahn serological reactions. The rôle of syphilis in producing specific types of aortitis is now well established; retrograde extension of the process is responsible for late involvement of the aortic valves and severe grades of aortic insufficiency are a common manifestation of tertiary syphilis.

There is apparently some disagreement of opinion in regard to the incidence of syphilis among the native Melanesians of these islands; the French Hospital authorities at Efati declared that the last survey made in 1935 showed a relatively high degree of population infection. Dr. Aisiri of the Fiji Medical School thought that the rate was rather low in comparison with certain southern states of this country. Other manifestations of tertiary syphilis with central nervous system or bone and joint involvement are rare; tabes is more or less unknown among the Melanesians.

The etiology of these aortic diastolic murmurs is thus open to some speculation; unless they are due to a disproportionately high incidence of syphilitic vascular disease, they must be the result of certain tropical infections, particularly yaws and perhaps chronic tsutsugamushi disease. The literature on the subject is not convincing, but this should prove to be a fertile field for research in tropical medicine since the late effects of both these diseases may subsequently appear in returning servicemen who have acquired these conditions while in the South Pacific.

No *presystolic murmurs* were discovered; rheumatic fever, if it occurs, must be very rare among the Melanesians. This is in rather sharp contrast with its occurrence among the other great racial stock of the South Pacific—the Polynesians. At Pago Pago in the American Samoas, through the courtesy of Capt. A. C. Dixon (MC) USN, I had the opportunity of examining several children with unquestioned rheumatic heart disease and two young women with mitral stenosis, one a native nurse at the Samoan Hospital.

Farther south, in New Zealand, the Maoris, who also come from pure Polynesian stock, have a relatively high incidence of rheumatic fever. At Dr. Alfred Dreifuss's clinic at Auckland I was privileged to see a number of cardiac Maori children. Here the incidence of rheumatic fever appears to be just as great among the Polynesians as among the European white group.

In published data this rate is approximately that of Atlanta, Ga. The Polynesians of the northern hemisphere as represented by the Hawaiians likewise have considerable rheumatic infection. At Honolulu I saw a number of rheumatic hearts among the pure Hawaiian group and the pathologic picture was not unlike that seen in the southern part of the United States.

The question whether acute rheumatic fever and rheumatic heart disease occur in the South Pacific has currently been the subject of some discussion; several papers have recently been published by authors who are not in complete agreement. I would hesitate to add to the confusion but the answer must be considered in three categories since it concerns three different groups of statistics. In my experience based upon a superficial survey made during 23 months' stay in the Pacific area, I would say that the Melanesians have little or no evidence of rheumatic infection whereas the Polynesians have a relatively high rate. The third group consists of the American servicemen, who, coming from all parts of the United States, have brought with them their own community's specific rate of infection. I have previously reported [2] the incidence of rheumatic fever among navy and marine-combat units at an advanced base in the South Pacific; in every instance there was a history of previous rheumatic infection. I did not see a single case of primary rheumatic fever, but there were many individuals who went through their second or third attack while in the tropics.

Angina Pectoris and Coronary Heart Disease

In view of the general prevalence of arteriosclerosis, the incidence of acute coronary thrombosis appeared to be exceedingly low; only one case of acute occlusion was seen, but the Native Practitioners reported that the condition was diagnosed from time to time. It was more frequent among the Melanesians living along or close to the sea coast than in those tribes that had settlements far in the hinterland of the jungle. It had not been seen in the hypertensive group previously described and it was not a common cause of death. On the other hand, in most of the cases with congestive heart failure, particularly in the older age groups, this was said to be due to chronic coronary disease.

Heart pain is not a common symptom among the natives; five French plantation owners who formerly employed large numbers of Melanesians to operate the huge cocoanut and copra industries agreed that compared to the other numerous complaints, the natives rarely reported pain in the heart. The Native Practitioners likewise said that angina pectoris was practically unknown; cardiac symptoms when they occurred were either related to dyspnea or heart consciousness in the form of palpitation. During the time that the native labor battalion was under observation, no one appeared at the field clinic for the relief of heart pain, but there were a few cases of dyspnea.

Congestive heart failure with edema of the legs and ascites is, however,

well known to the Melanesians; indeed many of their carved wooden figures show large rounded abdomens and greatly swollen legs. The early witch doctors were familiar with a number of digitalis-like substances which grow abundantly in the jungle. The water onion of the squill family and certain forms of *Cactus grandafloris* are favorite remedies for the treatment of anasarca. A tropical variety of fox glove called *gnopa* or *opa-opa* is employed by some of the Native Practitioners; this should not be confused with *po-po* (paw paw) or papyia, the seeds of which are said to be dangerous to those suffering from dropsy. There are several kinds of nuts which have a digitalis action; some of these like *thevetin* from the oleander tree and *trakis* from the lantern nut have been studied in this country. Nature has thus provided the Melanesians with many effective drugs for the treatment of congestive heart failure and the jungle folk lore is replete with cures obtained by their use.

Time and circumstance did not permit the study these individuals merited; the etiology should be more carefully investigated. Although a number of cases were probably the end result of advanced aortic valvular insufficiency, most were due to chronic coronary heart disease; the Native Practitioners estimated the ratio to be from 1 to 3 or 1 to 4. Some of this opinion was based upon postmortem material. The ritual of burial (clenumded) in certain tribes requires removal of the viscera and thus an opportunity for examination of the heart is given. The Fiji Medical School is noted for its well trained native physicians and their opinions have the respect of the entire South Pacific.* I did not see any of these hearts but from description they apparently showed considerable arteriosclerotic and atheromatous pathologic change with associated myocardial disease—the scarring from old myocardial infarcts and, in a few instances, well defined aneurysmal dilatation of the heart wall.

The interesting problem here is the predominance of so-called silent coronary disease among these primitive peoples and the possible explanation of why similar types of disease are associated with so much pain in the more civilized communities of the world. It is not that these Melanesians are less sensitive to painful stimuli as will be shown later; indeed their reactions to pain are usually quite child-like. I have seen robust men cry out at the prick of a jungle thorn, and no attempt is made to conceal painful feelings. But they pass through extensive coronary episodes without much, if any, pain. Why?

The question is provocative and more than academic; the answer can only be speculative. The entire problem of heart pain has never been satisfactorily explained notwithstanding the voluminous literature upon the subject and the huge amount of experimental work which has been done in the past 25 years upon the unraveling of the complex neurogenic network which involves the heart and aorta. One of the perplexing enigmas of

* See Dr. Samuel Lambert's splendid book, "A Yankee Doctor in Paradise."

internal medicine is the lack of correlation between coronary-cardiac pathologic lesions and the clinical symptoms produced by those lesions; two individuals with (apparent) identical lesions as the result of coronary disease may present entirely dissimilar clinical syndromes. This is especially true in regard to the pain factor.

In so-called "civilized communities" most patients suffer pain during a coronary episode; a few do not. Among the Melanesians the reverse is true; pain is not a conspicuous feature of the same disease, yet their threshold for painful stimuli is not unlike that of the average American or European. I will even go further, for the question of heart pain has always been of considerable interest to me. In an experiment to determine the relative skin, and bone and joint sensitivity of these natives, a group of very black negro members from a local CB unit volunteered to undergo the same tests; with the negroid habitus as a common denominator the experiment was a crude attempt to evaluate the pain response to the same stimulus in two groups of individuals: the one representing the product of modern civilization, the other from life in the jungle unaffected by the complexities and burdens of such civilization. The results of the experiment proved only one thing: there were no appreciable differences in the pain reactions of the two groups.

Superficially, therefore, civilization has done nothing to change the simple pain-mechanisms but *something* has been done to the deeper and more complicated receptor systems. What is this intangible factor which is responsible for the intense pain pattern in angina pectoris and acute coronary occlusion? Why is heart pain so much greater in the civilized individual and why is it more or less absent in these primitive peoples? What fields of research are opened by these questions! Can this *something* be psychosomatic in origin? We have but scratched the surface of the fundamentals of psychosomatic medicine. Modern civilization and psychosomatic phenomena go hand in hand; in a study of these Melanesians of the jungleland of the South Pacific may lie the key to a better and clearer understanding of many serious maladies which now afflict our communities. Of these, the degenerative cardiovascular diseases play the leading rôle in disability and death. From out of those steaming jungles, now the scene of warfare and bloodshed, may come the answer, let us hope, in a later, more peaceful world.

Peripheral Vascular Disturbances

Peripheral vascular disease is not unknown among the Melanesians; the pidgin word *dedfut* includes a variety of conditions involving the feet and lower legs. The natives regard any disabling condition that prevents them from walking as "dead foot." A number of tropical skin infestations produce ulcerations of the feet and great swelling occurs from the secondary infections and lymphangitis. Some of these extensive infections involve the veins and subsequently the arteries of the lower leg with massive thrombosis and occlusion. Gangrene of one or more toes is not uncommon and

occasionally the whole foot may be included in the process. I had the opportunity of examining two such legs which were amputated by Lieut. Jean Poulichan of the French Colonial Service at the Native Hospital at Espiritu Santos.

In one, a man age about 26, there had been a long history of severe pain in the great toe and sole of the right foot; from time to time large ulcerations appeared over the entire foot. These would heal and later break down again. The pain finally became so continuous and so severe that the man voluntarily begged Dr. Poulichan to cut off the foot notwithstanding the native prejudice against dismemberment of the body because of ritual tabu. The foot was so edematous that no pulsation could be felt in the dorsalis pedis but the posterior popliteals seemed to be normal. The leg was removed just below the knee. Dissection of the leg showed the artery and veins completely obliterated by dense scar tissue which bound the entire contents of the sheath together like a thick cord. Even the severed ends of the arteries showed considerable sclerosis of the walls and much reduced lumina. The bones of the foot were atrophied and there seemed to be an extensive type of proliferative osteoarthritis involving the whole ankle joint.

The other case was less severe; this man was about 35 years old with a very long history of pain in the lower leg and toes, perhaps of 10 years' duration. Trophic ulcerations had occurred several times and healed slowly. At the time the leg was amputated there were only a few open skin areas but the pain was becoming unbearable. On examination there was no dorsalis pedis pulsation on either foot. All of the peripheral arteries appeared to be prematurely thickened and sclerosed; the blood pressure was normal. The man was very loquacious about the foot: "Dedfut he too damn much burn-burn; sam time slep no-no much lon-lon. Cartem oop off." (The sick foot now is paining me like it was burned all over but at the same time it feels as if it was asleep for a long time. Cut it off as you would cut off the foot of an animal.) Amputation was performed just below the knee; dissection here showed a chronic inflammatory process involving the artery and veins in the sheath. There was some obliteration of the lumen of the artery but the veins were completely occluded. Grossly, the condition resembled a type of Buerger's disease, but the possibility of a chronic suppurative pathologic process with secondary vascular changes could not be eliminated without better laboratory facilities than were available.

Dr. Aisari, the Native Practitioner assigned by the Fiji Medical School for service in the New Hebrides, said that peripheral vascular disease was not uncommon but frequently it was so intimately associated with various tropical infestations of the feet that it was difficult to determine which condition was primary. The diagnostic evaluation of the pain factor was important; where the pain was out of proportion to the obvious degree of inflammatory changes, he always suspected an underlying vascular disturbance, since many badly infected feet had little or no pain. He thought,

however, that certain tropical infections might be responsible for vascular changes of the lower legs and feet and the secondary lowered resistance following the lessened blood supply completed the vicious circle ending in trophic ulceration and re-infection.

Varicose Veins. No account of the vascular diseases of the Melanesians would be complete without some comment upon the rather high incidence of varicosities of the lower extremities. Individuals of all ages, from children to the oldest, seemed to have some degree of venous disease. This may have been due to secondary changes in the veins of the lower legs as the late result of continuous re-infection of the feet by various tropical organisms. The natives use no protection for the soles of the feet and are bare footed throughout their lives. Although the soles of the feet are covered with an extremely thick cornified skin, the dorsum of the foot and the ankles have no such protection and are subject to scratching and cutting by coral and sharp spiculed jungle vegetation.

Here again it is difficult to determine the different steps in the evolution of the ulcerations; some seemed to be rather typical varicose ulcers, but others were better classified as tropical or jungle ulcers with a chronicity which obscures the basic disease. Many American servicemen developed ulcers of this kind as the result of trauma, usually by coral abrasion, with a secondary fungus infection. These presented a problem in therapy and in many instances the disability constituted a serious loss of front line man power. The natives, however, regard these ulcerations with complete indifference and looked with some amusement when dressings were applied to keep the wounds clean; perhaps to some extent, they were right, for those ulcers which were kept clean and exposed to the sunlight seemed to fare as well as those treated by one combination of chemicals or another.

Comment

After our return to the advanced naval base from whence the recruiting unit started, I had an opportunity to go over the notes which I had made during the expedition through the various islands and to formulate certain opinions. The purpose of the trip has already been made clear and the territory covered, although extensive in itself, constitutes but a small part of the vast area west of the international date line and south of the equator known as "the South Pacific." The facts gathered and the impressions gained are thus predicated upon our own experiences and at best represent but a modest sampling of the Melanesian natives as we saw them in the island groups of the New Hebrides and Solomons. I would not want any statement made in this report to be construed as a final authoritative opinion upon any of the various conditions discussed. Such a report would necessitate a survey of much greater scope both in time and resources and over a considerable area not included in this expedition; such a survey would include the study of many more Melanesian groups—from the pigmies of

western Espiritu Santos to the giants of Matakanta, as well as the fabulous albinoes of Bonokula.

With these limitations in mind certain conclusions are, perhaps, permissible. First and foremost is the surprisingly high incidence of cardiovascular disease of all types found among these primitive peoples of the jungles; this is particularly true of the degenerative types of heart and blood vessel disease. I have used the word *surprisingly* for the conditions found were contrary to current thought and teaching. Throughout the literature upon arteriosclerosis, coronary heart disease, and hypertension is the constant repetition of the major rôle played by the stress of civilization in the development of these conditions. The psychosomatic reactions to business and social demands and the constant pressure of individual adjustment to a changing environment have been held responsible for the great increase in the cardiovascular degenerative diseases of the past several decades.

Yet the incidence of these very same diseases is also relatively high among a people whose entire life is more or less free from such alleged pernicious factors. To be sure, life in the jungle may be beset with a number of nature-made fears and man-made taboos but it is doubtful that the intensity of psychosomatic reaction to environment is anywhere as great among the Melanesians as among individuals in an average American community. What, then, can account for the development of these degenerative "civilized diseases" under a primitive way of living?

The jungle abounds with infections and infestations; in addition to the host of specific tropical diseases like malaria, yaws, tsutsugamushi fever, dengue, and sand-fly fever, all of the microörganisms known in the temperate zone thrive with unusual virulence in the tropics. Diphtheria, tuberculosis, meningococcus meningitis, pneumococcus pneumonia, tetanus, gas gangrene as well as the gastrointestinal infections like typhoid, dysentery, cholera, hookworm and the other parasites, all reach a high degree of malignancy in the jungle. Survival must be due only to immunological processes of much greater humoral potency than that common to similar infections in this country; can these high titer antibodies have a primary destructive effect upon the heart and blood vessels? And can the subsequent reactive pathologic changes be responsible for the degenerative changes seen in the cardiovascular system in later life?

Infection has long been recognized as an important contributing factor in the development of these degenerative heart and blood vessel diseases in civilized communities. It is said, however, to have a minor rôle compared to the wear and tear of the psychosomatic factors. Have we now sufficient evidence to attempt a balance sheet? Can we evaluate the relative importance of infection and a way of living and say that in the jungle degenerative cardiovascular disease is the result of *major* infection and *minor* psychosomatics and in civilized communities the equation is reversed to *minor* infection and *major* psychosomatics? Is the problem more than one of academic speculation?

Finally, a word about the acute and more immediate results of the tropical diseases upon the heart. Although rheumatic fever is almost unknown among the Melanesians, valvular heart disease does occur. The aortic valvular mechanism is chiefly involved; this may be the result of syphilis or the syphilis-like jungle infections. Other diseases like malaria, yaws, and tsutsugamushi fever are said to cause heart disorders. I have previously reported the effects of dengue upon the heart.[3] Congestive heart failure following aortic valvular insufficiency is well known to the natives but the common cause of dropsy is chronic coronary heart disease for which, fortunately, the jungle provides an abundance of digitalis-like substances.

Summary

1. During the early days of the war in the South Pacific, the need for native labor to supplement the work of the Naval Construction Battalions became a necessity. A recruiting unit to select the most desirable Melanesians had, in the course of its program, visited many of the islands of the New Hebrides and Solomons groups. Some of these islands, like Malakula, are perhaps the most primitive unexplored spots left in the world.

2. Since the jungle native is valuable as a member of a labor battalion only in direct proportion to his health, the medical examination of all candidates was of major importance. An unusual opportunity of examining many natives was thus presented; this also included women and children. The latter groups were seen chiefly as a gesture of good will to promote friendly relationships between the natives and the American forces of occupation. Altogether, many hundreds of primitive peoples were seen and many were carefully examined.

3. As a cardiologist, I was particularly interested in various types of heart and blood vessel disease which were discovered. Since many cardiovascular disturbances are said to be the result of modern civilization, an opportunity was given here to evaluate certain well known forms of heart disease in a jungle background. The following observations are thus purely personal, supplemented by opinions expressed by the kindly Native Practitioners and the courteous personnel of the French Colonial Service.

4. Arteriosclerosis and vascular degenerative diseases are common; inhabitants of the jungle age quickly and die in the 40's and 50's.

5. In general, blood pressure levels are not dissimilar to those found in Americans or Europeans of equal age, weight, and sex. However, a small group of Melanesians was discovered with hypertension; most of these were interrelated. High blood pressure in others seemed to be associated with previous renal damage as the result of black water fever and other tropical infections. Hypertensive cerebral accidents are known to the natives.

6. Simple cardiac hypertrophy is common; it was apparently unrelated to any discoverable type of heart disease.

7. Irregularities of the heart were also found. Most of these were sinus tachycardia with high rates. Extrasystolic arrhythmias were the next most common. One case of auricular fibrillation was seen and paroxysmal tachycardia was said to occur.

8. Heart murmurs were discovered. These were classified chiefly as functional systolic pulmonic murmurs. Apical systolic functional murmurs were next in frequency. A group of aortic valvular diastolic murmurs were seen; the etiological background of the pathologic lesions in these caused considerable speculation. Were they due to syphilis or the syphilis-like tropical infections? No presystolic murmurs were found; rheumatic fever is rare among the Melanesians compared to the Polynesians who are the other great racial stock of the South Pacific.

9. The typical syndrome of acute coronary occlusion with pain or angina pectoris is rare; on the other hand, chronic coronary heart disease is common. The latter is the cause of most of the cases with congestive heart failure. The natives have many digitalis-like jungle remedies for the treatment of dropsy and they are familiar with this condition as is shown in their primitive wood-carved ceremonial figures.

10. The absence of the pain pattern in these coronary syndromes led to experiments to determine the pain threshold of the natives compared to negro personnel from a local CB unit; there was no material difference in the two groups. The psychosomatic mechanisms developed by life in civilized communities may be the answer to this important question. The problem merits investigation since it bears directly upon the concept of heart pain.

11. Peripheral vascular disease was also seen; these cases were probably due to the high incidence of arteriosclerosis and atheromatosis and the secondary results of jungle infestations of the feet or a combination of both. Varicose veins and thrombophlebitis are common.

12. Cardiovascular disease appears to be about as frequent among the primitive peoples of the South Pacific islands as among Americans and Europeans. There are some differences, however, in the distribution of the various types of heart and blood vessel conditions but most of the diseases of the cardiovascular system seen in civilized communities are also found in the jungle.

BIBLIOGRAPHY

1. Hyman, A. S.: Clinical masquerades of malaria, U. S. Naval Med. Bull. To be published.
2. Hyman, A. S.: Cardiovascular disease in the tropics, U. S. Naval Med. Bull., 1944, xlii, 545.
3. Hyman, A. S.: The heart in dengue, War Med., 1943, iv, 497.

THE COMPARATIVE VALUE OF SEVERAL LIVER FUNCTION TESTS *

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THE present dissatisfaction with liver function tests is largely dependent upon a tendency to rely solely upon the result of one particular liver function test, disregarding such factors as the multiple functions of the liver, its regenerative ability or the type of injury. It is obvious that in an organ with multiple functions, such as the liver, the result of a single test may be negative in the face of damage so extensive that it can be ascertained without any laboratory procedures. Such a negative result means only that the test chosen measured a function not as yet altered in that particular diseased liver. The value of any single liver function test, when used, is directly proportional to an appreciation by the user of the function it is testing.

It is highly important to determine whether or not the liver is injured and, if so, the type of injury present. To determine such facts, the limitations of the several liver function tests must be kept in mind so that a proper choice of one or more of them can be made and the results of the tests properly interpreted in the light of physiological or pathological change. If such criteria are used, the results of liver function tests, properly applied and interpreted, often enable one to diagnose impaired liver function early in its course and, at times, to predict correctly the type of lesion present and the general course the disease is following.

Much of our knowledge of the comparative value of liver function tests is based upon the studies of one or two tests done upon a series of patients and a comparison of the results with those of other tests performed upon other patients, by the same, but more often, by different investigators. Though this method of comparison may be entirely accurate, theoretically it lends itself to several sources of error. There may be differences in the personal estimation of the extent and degree of the disease. There may be differences in the classification of liver disease in various clinics with the difficulty incident to the interpretation of one classification in terms of another. There may be minor differences in the technic of performing and interpreting the tests themselves. To avoid these sources of error, we have performed eight different liver function tests at approximately the same time upon each of 153 patients with various types of suspected liver disease. In many of these cases there was neither conclusive clinical nor laboratory evidence of liver disease and hence the results of the liver function tests in the whole

* Received for publication December 10, 1943. From the Department of Internal Medicine, Medical School, University of Michigan.

† Contribution to this communication preceded entry into the Army of the United States.

group are not reported at this time. More than 50 of the total number of patients studied presented what we believed to be clinical or proved pathological cases of cirrhosis, neoplasm or hepatitis. The results of liver function tests in these cases can best be dealt with under the headings of the tests.

Urinary Urobilinogen Test. It is now generally accepted that urobilinogen is a pigment formed by the bacterial reduction of bilirubin in the intestinal tract. A large part of the urobilinogen formed is excreted in the stool. Some is absorbed from the intestine and reconverted by the liver into bilirubin. A small amount is excreted in the urine. In the presence of cellular liver disease the amount of unconverted urobilinogen in the blood increases and is excreted by the kidneys. Because of the increased excretion of urobilinogen by the kidneys in some forms of liver diseases, its quantitative estimation in the urine may be of value in determining the presence and extent of cellular liver disease. In using such a test, however, two factors must be kept in mind. In spite of normal hepatic cellular activity there may be an abnormal degree of urobilinogenuria associated with increased blood destruction; the normal liver cannot cope with this demand to convert an abnormally large amount of blood pigment into bilirubin at the usual rate. Furthermore, in chronic renal disease the test is of no value because the kidneys cannot excrete the pigment.

In carrying out this test, we have used a modification of the method described by Wallace and Diamond.[1] Distilled water is added to fresh urine specimens to make dilutions of 1:10, 1:20, 1:40, 1:80, 1:160, etc. To 25 c.c. of each of these dilutions is added 2 c.c. of Ehrlich's reagent. A cherry pink color slowly develops which is best seen by looking down through the tube. Readings are made in five minutes. Normally, the appearance of the characteristic color is rarely seen in dilution above 1:20. In this study the presence of this color in any dilution above 1:40 was considered to be abnormal.

In a series of 57 patients with definite liver disease shown in table 1, 43

TABLE I

Results of the *Urobilinogen Test* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with Negative Tests with Direct *VdB.*	Corrected Per Cent Positive
Cirrhosis	41	34	82.9	2	87.2
Neoplasm	6	4	66.7	1	80.0
Hepatitis	10	5	50.0	3	71.4
Total	57	43	75.4	6	84.3

or 75.4 per cent had abnormal excretions of urobilinogen. In the neoplasm and hepatitis groups there were fewer abnormal excretions of urobilinogen than in the cirrhosis group. When the blood bilirubin determina-

tions are compared with the negative urinary urobilinogen tests, it is noted that in the cirrhosis group, two patients had direct van den Bergh reactions. In the neoplasm group, one patient had a direct van den Bergh reaction. When parenchymatous disease of the liver becomes so extensive that obstructive jaundice occurs, bilirubin does not appear in the gastrointestinal tract and the urobilinogen test is of no value as an index of liver disease.

In the absence of an obstructive jaundice and in cases where other causes of urobilinogenuria can be ruled out, the presence of urobilinogen in the urine in dilutions greater than 1:40 is significant. The test is easily and rapidly performed and may help in making a diagnosis of liver disease. Because the test is roughly quantitative it also has value in determining the progress of liver injury.

Van den Bergh Reaction. The presence or absence of a hyperbilirubinemia is always important in liver disease, and the quantitative van den Bergh reaction is probably the most commonly used single liver function test. Pathologically, a hyperbilirubinemia means either an obstruction of the bile ducts, an inability of the parenchymal liver cells to excrete all of the bile brought to them, or production of bile pigment from blood destruction, greater than the liver can excrete.

Van den Bergh and Muller [2] showed that in obstructive jaundice the characteristic color occurred promptly upon the addition of the diazo reagent to the blood serum whereas in hemolytic jaundice the color appeared only after alcohol was added. These reactions were thereafter called direct and indirect. Later Feigl and Querner [3] noted that some sera developed color upon the addition of the diazo reagent and the intensity of the color increased as the mixture was allowed to stand. The importance of the direct and indirect reactions cannot be overemphasized in the interpretation of the van den Bergh test. Barron [4] has shown that bilirubin, which has passed through the epithelial cells of the liver and is regurgitated into the blood stream, will give a "direct" reaction. In this state it is free bile and is readily excreted by the kidneys. Bilirubin which has not passed through the liver cells gives an "indirect" reaction because, as Barron has shown, it is adsorbed by the serum proteins. In this state it is not readily excreted by the kidneys. The biphasic or "delayed direct" reaction then indicates both free and protein-adsorbed bilirubin in the blood stream and suggests both obstruction of the large bile ducts or small intrahepatic channels and reduced cellular activity of the liver.

The quantitative van den Bergh reaction is of greater value in determining the amount of jaundice than it is in estimating the presence and severity of liver disease. Frequently an extensive impairment in liver function may exist without jaundice and likewise severe jaundice may exist without liver damage. Soffer has emphasized the value of the van den Bergh reaction in following the course of liver disease by showing that in the early stages an indirect reaction is present which later may become biphasic and then direct

as the lesion progresses. Improvement may be indicated by a direct reaction becoming biphasic and then indirect.

Table 2 shows that in 58 cases of cirrhosis, neoplasm and hepatitis, the van den Bergh reaction was positive * in 30 or 51.7 per cent. There were 21 direct, no indirect, and nine delayed direct or biphasic reactions. Approximately 48 per cent of the cases of known liver disease had normal van den Bergh reactions.

Galactose Tolerance Test. Galactose has been chosen as a substance to measure the carbohydrate function of the liver because there is no renal threshold for its excretion, the endocrine glands have no effect on its metabolism, and it is not utilized by tissues other than the liver.

The test is simply and quickly done by the method described by Shay, Schloss, and Rhodis.[5] After a 12-hour fast a specimen of urine is collected and tested for sugar. Forty grams of powdered galactose are given orally

TABLE II

Results of the *Van den Bergh Reaction* in 58 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Type of Reaction		
				Direct	Indirect	Biphasic
Cirrhosis	41	17	41.5	12	0	5
Neoplasm	6	4	66.7	2	0	2
Hepatitis	11	9	81.8	7	0	2
Total	58	30	51.7	21	0	9

and urine specimens collected at hourly intervals for five hours. No food is ingested during this period, but water may be taken freely. The five urine samples are then pooled and the amount of sugar determined by the quantitative Benedict method. From this is calculated the quantity of galactose excreted in the urine. A total elimination of three grams or more of galactose is an indication of hepatic disease.

This test is least satisfactory in determining whether or not liver disease exists. Its main value seems to be in the differentiation of a diffuse cellular intrahepatic lesion from other types in which disease is due to an extrinsic obstruction or when considerable regeneration has taken place. In patients with considerable jaundice, the galactose tolerance test may prove valuable *early* in the disease. When jaundice is due to hepatitis, a positive test is proof of cellular damage. When the test is negative early in the disease, it may be of no significance. Later in the course of such a jaundice, the test is often of less value because regeneration of liver cells occurs so rapidly that the test may be negative. Once a test is positive, however, it offers distinct aid in following the course of the cellular injury.

* In our series indirect van den Bergh determinations of over 7 mg. per 1,000 c.c. (0.7 per cent) and those showing direct or biphasic reactions were considered abnormal.

Table 3 illustrates our results with the galactose tolerance test. Although this is not a large group, it shows that when a diffuse hepatitis is present the galactose test is more likely to be positive than when cirrhosis or neoplasm is present. In cirrhosis, the test is more apt to be negative because the process is not acute, regeneration of the liver structure is constantly occurring, and diffuse cellular disease is a late occurrence. In neoplasm much of the liver is apt to be uninvolved and may function normally. Our experience with the test shows that it is not a good test to determine the presence or absence of liver disease. It is more likely to be positive in diffuse cellular disease (hepatitis) with jaundice than in other forms of intrinsic liver disease, but it will be noted that only approximately 25 per cent of the patients with jaundice had positive galactose tests and nearly one-half of the positive galactose tests were in patients who were not jaundiced at the time the tests were done. Jaundice is an indication for the test

TABLE III

Results of the *Galactose Tolerance Test* in 54 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients Jaundiced	Number Positive	Number Positive in Patients Not Jaundiced
Cirrhosis	38	7	18.4	15	4	3
Neoplasm	6	1	16.7	2	0	1
Hepatitis	10	3	30.0	8	2	1
Total	54	11	20.4	25	6	5

but the time at which the test is done during the period of jaundice is more important, and a negative test does not necessarily exclude liver injury. Likewise, the test may be positive, in the absence of jaundice.

Glucose Tolerance Test. Because one of the major functions of the liver is the conversion of glucose to glycogen and its storage, hepatic disease may in some instances produce a disturbance in its metabolism.

Chloroform or phosphorus poisoning or partial hepatectomy in animals produces an atypical blood sugar response. After the removal of 75 per cent of the liver, the glucose tolerance curve deviated from the normal in two ways: it tended to resemble the diabetic type of curve and the fasting blood sugar was low. It has been observed that with damage to the liver, the storage of glycogen may be considerably impaired and when an excess of carbohydrate is given it accumulates in the blood stream and is excreted by the kidney. The presence of a high blood sugar stimulates the production of insulin and with the increased combustion of glucose in addition to its loss through the kidney, a hypoglycemic reaction may occur during the third, fourth or fifth hour after a high carbohydrate meal. Furthermore, because the glucose tolerance test is a routine laboratory procedure, we have

been interested in its value as an index of liver function and have performed glucose tolerance tests on our patients. The standard method was employed, using 1.75 gm. of glucose per kilogram of body weight. Patients manifesting diabetes mellitus in addition to their liver disease have not been included in our series.

Table 4 shows that in 54 patients, the glucose tolerance curves were abnormal in 38 or 70.4 per cent. Eight (14.8 per cent) had spontaneous glycosuria. Twelve (22.2 per cent) had blood sugar determinations of 41 mg. or less per 100 c.c. of blood. Five (9.3 per cent) had one or more spontaneous hypoglycemic attacks. Thirteen (24.1 per cent) had fasting blood sugar determinations of 70 mg. or less per 100 c.c. of blood; seven (12.9 per cent) had fasting blood sugar determinations of 71, 72, or 73 mg. per 100 c.c. of blood; and 25 (46.3 per cent) had either fasting blood sugar determinations of 73 mg. or less per 100 c.c. of blood or blood sugar determinations during the third, fourth or fifth hours of the tolerance test

TABLE IV

Results of the *Glucose Tolerance Test* in 54 Patients with Known Liver Disease

Disease	No. of Patients	Number Positive	Per Cent Positive
Cirrhosis	38	25	65.8
Neoplasm	6	4	66.7
Hepatitis	10	9	90.0
Total	54	38	70.4

of 41 mg. per 100 c.c. or lower. Seven had both. Twenty-six (48.1 per cent) had either fasting blood sugar determinations of 73 mg. or lower per 100 c.c. of blood or hypoglycemic attacks. Four patients had both. Only fourteen patients (25.9 per cent) had normal glucose tolerance curves, no spontaneous glycosuria, no hypoglycemic attacks, and normal fasting blood sugar determinations.

Inasmuch as the glucose tolerance tests were done on the same patients who also had galactose tolerance tests, we are able to compare the relative value of each test. It appears that if the glucose tolerance test begins with a normal or low fasting blood sugar, elevates during the first or second hours to a level higher than normal and then falls to a hypoglycemic level during the third or fourth hour, it is probably indicative of liver disease. Glycosuria may be present during the test and hypoglycemic reactions may also occur. Not uncommonly both reactions are seen in the same patients. A comparison between the value of the galactose tolerance test and the glucose tolerance test shows that the latter is a much more delicate test of liver disease. The glucose tolerance test shows the same tendency, in a greater degree, to require extensive liver cell disease and as a result is an important test to use in differentiating hepatitis from obstructive jaundice.

Serum Proteins in Liver Disease. A. Blood Serum Protein Determinations. A reduction of the level of serum proteins has been noted in liver disease by many authors. Though it is generally accepted that the serum proteins are synthesized in the liver, there still is insufficient experimental proof that this is true. It has been shown that when animals were given phosphorus and carbon tetrachloride, a decrease in the serum proteins followed the liver injury. Furthermore, it is known that reduction of the serum proteins may be nutritional in origin and that there is a relationship of the serum protein production to vitamin B_1.

In considering the level of serum proteins as an index of liver function one must also keep in mind that hypoproteinemia is often associated with renal disease and with undernutrition. The serum albumin is most often affected and the serum globulin may be elevated. The albumin-globulin ratio may approach unity or may be reversed. Total protein concentration under 6.5 gm. per cent and serum albumin concentration under 4.0 gm. per cent were considered abnormal.

Table 5 shows that 48 out of 57 patients (84.2 per cent) had a reduction of the serum albumin level below 4.0 grams. From this table one can infer

TABLE V

Results of the *Serum Protein Determinations* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number with Albumin Concentration under 4.0 grams per cent	Per Cent Positive	Number with Total Protein under 6.5 grams per cent	Per Cent
Cirrhosis	41	33	80.5	21	51.2
Neoplasm	5	5	100.0	4	80.0
Hepatitis	11	10	90.9	7	63.6
Total	57	48	84.2	32	56.1

that hypoalbuminemia may be a good index of liver disease. It is especially valuable in indicating damage to the liver in neoplasm and cirrhosis, in which the galactose and glucose tolerance tests are of less value. It seems to be a more delicate test than those yet considered and is independent of the presence or absence of jaundice.

B. Takata Ara Test. In 1925 Takata [6] and later Takata and Ara [7] noted that when chest fluid from a patient with lobar pneumonia was added to a solution of sodium carbonate, mercuric chloride and acid fuchsin, a precipitate of mercuric oxide occurred. They believed this precipitation was due to the globulin fraction of the exudate. Later Staub [8] suggested the use of this test in cirrhosis of the liver, and since then it has been used extensively as a liver function test. Jezler [9] found that the total serum protein content played no rôle, but that the reaction was dependent upon the globulin content of the fluid. He found it positive in widespread parenchymal liver disease.

Table 6 shows that the test was positive in slightly more than half of the cases (51.8 per cent), but it is not a specific test for cirrhosis, as has been claimed, and it may be negative with known liver disease present. An analysis of the figures of table 6 shows that of 36 patients with albumin: globulin ratios of 1 or under, 22 had positive Takata Ara tests. In 19 patients with albumin-globulin ratios over one, seven had positive Takata Ara tests. In 14 of the 27 tests reported negative, the albumin-globulin ratio was 1.0 or less. Of 15 patients in whom the bromsulphalein showed a 35 per cent retention or less, indicating a mild impairment of liver function, the Takata Ara test was positive in only three cases. In 13 instances in which the van den Bergh reaction was indirect and the bromsulphalein showed more than a 35 per cent retention of the dye, 12 individuals showed a positive Takata Ara test. Our figures compare favorably with those of more recent authors who feel that the Takata Ara test is dependent upon the globulin fraction but the reaction is not necessarily positive when the

TABLE VI

Results of the *Takata Ara Test* in 56 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with A/G 1.0 or under	Number Positive	Number of Patients with A/G over 1.0	Number Positive
Cirrhosis	41	20	48.8	26	15	15	5
Neoplasm	6	3	50.0	4	3	1	0
Hepatitis	9	6	66.7	6	4	3	2
Total	56	29	51.8	36	22	19	7

albumin-globulin ratio is reversed. Although most of the positive tests (22 out of 29) showed a reversal of the ratio, 50 per cent of those that showed a negative Takata Ara test also had a reversal of the ratio. In comparing the Takata Ara test with the severity of the hepatic lesion as measured by the bromsulphalein test, it can be seen that the test is positive in the more advanced cases of liver disease, but a positive test does not necessarily imply hepatic damage.

Bromsulphalein Test. In 1909 Abel and Rowntree [10] showed that when injected into the blood stream, phenoltetrachlorphthalein dye was removed by the liver and excreted almost entirely into the bile ducts. Later Whipple, Mason and Peightal [11] demonstrated that when experimental liver injury was produced in animals, the rate of elimination of this dye was directly proportional to the injury. Rosenthal [12] did some similar experiments and then, after injection of the dye, determined its concentration in the blood stream at varying intervals. He suggested that it might be used as a liver function test. Rosenthal and White [13] later used various other halogen substitutes for the chlorine part of the original dye and also found that sulphonation of

the dye prevented its diffusion into the tissues where, later, it was picked up by the liver. As a result they recommend the use of phenoltetrabromphthaleinsulphonate or bromsulphalein. The difference in the action of the original dye and the sulphonated dye is probably due to the former being a colloid and the latter a crystalloid. The weakness in the use of the dye, however, lies in the fact that it is excreted through the bile passages into the intestinal tract. Any lesion, extrinsic or intrinsic, causing obstruction of the bile passages, will delay the excretion of bromsulphalein. In cases of obstructive jaundice due to neoplasm of the ducts, stone, severe hepatitis where the bile ducts may be closed, advanced cirrhosis or acute yellow atrophy, the results of the bromsulphalein tests are not true indices of liver damage when the quantitative van den Bergh reaction is direct. Any direct or biphasic van den Bergh reaction means obstruction and renders the test valueless.

The test is done as follows: 5 mg. of bromsulphalein per kg. of body weight are injected intravenously. A sample of venous blood is collected in 30 minutes, centrifuged, and the serum divided into two parts. One part is alkalinized with two drops of 10 per cent NaOH and compared with a set of color samples indicating the per cent of the dye present in the blood at that time. The second sample, acidified with one drop of HCl, is placed behind the standard color tubes to give a similar background in comparing the unknown. In 57 cases of cirrhosis, neoplasm and hepatitis there were 29 with indirect van den Bergh reactions. Twenty-five of the 29 cases, or 86.2 per cent, had bromsulphalein determinations that were considered abnormal. Retention of more than 15 per cent of the drug in 30 minutes was considered abnormal. It will be seen in table 7 that the test is non-

TABLE VII

Results of the *Bromsulphalein Dye Excretion Test* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with Indirect *Van den Bergh*	Number Positive	Per Cent Positive
Cirrhosis	41	37	90.2	25	21	84.0
Neoplasm	6	6	100.0	2	2	100.0
Hepatitis	10	9	90.0	2	2	100.0
Total	57	52	91.2	29	25	86.2

selective and more delicate than any procedure yet considered for determining liver disease. The results are in agreement with those of other investigators who believe that in the absence of jaundice, the bromsulphalein test is the most valuable test in determining the presence of parenchymatous liver injury. The negative tests in undoubted cases of liver disease, as noted in table 7, are indications that the test is not infallible. If positive, the brom-

sulphalein reaction means some degree of liver injury. If negative, it does not necessarily eliminate the possibility of liver damage.

Macrocytosis as Index of Liver Disease. Since the work of Castle, it is generally accepted that the substance necessary for the maturation of red blood cells is formed from the interaction of an extrinsic factor (food) with an intrinsic factor present in the stomach. The resulting product is absorbed from the intestine, stored in the liver and utilized when needed. Disturbance of this mechanism at any point will produce a macrocytic anemia.

Wintrobe and Shumacker [14] reported a large series of cases of macrocytic anemia in liver disease and, since their work, many similar observations have been recorded. It has been shown that the liver is the storehouse for the material necessary for the maturation of the red blood cells.

A macrocytic anemia may occur in pernicious anemia, syphilis or cancer of the stomach, gastrectomy, pregnancy, obstruction of the intestine, fish tape worm infestation, celiac disease, gastrocolic fistula, and sprue. If these conditions are ruled out, the presence of a macrocytic anemia may indicate liver disease. In these cases, the anemia is seldom as severe and the variation in the cell sizes may be less marked than in pernicious anemia.

The results of mean corpuscular volume determination on 41 cases of cirrhosis, six cases of neoplasm and 11 cases of hepatitis are shown in table 8.

TABLE VIII

Results of the *Mean Corpuscular Volume* Determinations in 58 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive
Cirrhosis	41	26	63.4
Neoplasm	6	1	16.6
Hepatitis	11	5	45.5
Total	58	32	55.2

It will be seen that in cirrhosis, where the disease process is quite extensive, the incidence of macrocytosis is greater than in neoplasm of liver where large amounts of the hepatic tissue may be normal. In hepatitis, where the process is often acute, regeneration is apt to be quite rapid, and the incidence of macrocytosis is less frequent than in cirrhosis. The test is quickly done, valuable in various types of liver disease, and quite indicative, when positive, of extensive liver damage when other causes of macrocytosis can be ruled out.

DISCUSSION

The relative value of any of the eight liver function tests used in this study, in cirrhosis, neoplasm and hepatitis can be seen in table 9. Inasmuch as all of these tests were done on the same patients at approximately the same

TABLE IX

Results of All Tests in Known Liver Disease

Disease	Number of Patients	Galactose Tolerance Test	Van den Bergh Reaction	Takata Ara Test	Mean Corpuscular Volume	Glucose Tolerance Test	Urobilinogenuria		Serum Proteins		Bromsulphalein	
							Total	Corrected	Hypoalbuminemia	Hyperproteinemia	Total	Indirect Van den Bergh
Cirrhosis	41	18.4	41.5	48.8	63.4	65.8	82.9	87.2	80.5	51.2	90.2	84.0
Neoplasm	6	16.7	66.7	50.0	16.6	66.7	66.7	80.0	100.0	80.0	100.0	100.0
Hepatitis	11	30.0	81.8	66.7	45.5	90.0	50.0	71.4	90.9	63.6	90.0	100.0
Totals known liver disease	58	20.4	51.7	51.8	55.2	70.4	75.4	84.3	84.2	56.1	91.2	86.2

time, a comparison of their worth can be made. It can be seen that the galactose tolerance test was positive in only 20.4 per cent of the cases, whereas the van den Bergh reaction showed jaundice in 51.7 per cent and the serum proteins were abnormal in more than 84 per cent. The galactose tolerance test may be valuable in differentiating an extrinsic obstructive jaundice from an intrinsic diffuse cellular hepatitis, but its efficiency in doing so is very low. However, it is to be remembered that the test may be positive in the absence of jaundice. The glucose tolerance test is a far better test to use if such a differentiation is desired, for it was positive in 90.0 per cent of our cases of hepatitis whereas the galactose tolerance test was positive in only 30.0 per cent. The van den Bergh reaction is the most established of all the liver function tests and the most universally used. Unfortunately it loses much of its value in differentiating the various types of liver disease if the other causes of increased blood bilirubin are not kept in mind and if the direct, indirect or biphasic reactions are not determined. Alone, it means only that the patient does or does not have jaundice, and if jaundice is present, whether it is an obstructive jaundice, non-obstructive jaundice or a combination of both. It has some value in prognosis, by the character of its reactions, when several determinations are made. The reaction may be normal with advanced liver disease.

The Takata Ara reaction is non-specific and, although it was positive in only about half of our patients, when positive it meant advanced liver disease. In this regard, the test has merit in allowing a prognosis of the severity of the parenchymatous disease. The determination of the mean corpuscular volume is, probably, not a good test for liver function. It was a poor index of disturbed function in neoplasm and was not as good as other tests in hepatitis. The importance of our determinations seems to lie in the relative frequency of macrocytosis occurring in cirrhosis and emphasizes the fact that, if other common causes of a macrocytic anemia can be ruled out, liver disease should be suspected.

The glucose tolerance test has been little used and much maligned as a liver function test. If the curve is interpreted in the light of the physiological findings reported after destruction or removal of large parts of the liver parenchyma, it seems to have definite value as a liver function test. Its simplicity and general use make it a good test. In our series, it was fourth in importance as an index of disease and either as good as or better than all other tests in hepatitis. It is independent of jaundice and hence has importance when the bromsulphalein or urinary urobilinogen tests are of no value.

The urinary urobilinogen test is seldom used but because it is simply done and is an easily performed office procedure, its relative importance as an index of disturbed liver function should be carefully appraised. It can be roughly quantitative and when positive, has value, at least, in pointing to possible liver disease. If other causes of increased urobilinogen are

absent, a positive test immediately warrants further liver function studies. It is a non-specific test and as such only points to the liver as a probable cause of the disturbed urobilinogen excretion. In the presence of jaundice, the test is worthless. It is a good test to combine with the van den Bergh reaction.

The determination of the serum proteins is now being used to a greater extent as a liver function test. Its non-specific nature, however, gives it the same relative value as the bromsulphalein test. Its apparent independence of jaundice enhances its value. When obstructive jaundice is present, our figures show it to be the most delicate test of all those used. Because so little is known about the origin of the serum proteins and the various conditions that may alter it, the value of their determination in liver disease must await further fundamental work.

The bromsulphalein test is the most sensitive of all the eight liver function tests *in the absence of* obstructive jaundice, although it is not infallible. Its quantitative character makes it particularly valuable in following the course of the liver disease during the period when the patient is free of obstructive jaundice. When obstructive jaundice appears, other tests must be used to determine prognosis.

Conclusion

1. In patients who are jaundiced, the best tests to use for the estimation of hepatic function are the serum protein determination (hypoalbuminemia) and the glucose tolerance test. Invariably such patients will have had a van den Bergh test already performed.

In patients who are not jaundiced, it appears that the best tests to use are the bromsulphalein dye excretion test and the urobilinogen test. In these patients the van den Bergh, too, will already have been performed.

In either situation, the other tests may well add further information regarding the degree of impairment of hepatic function.

2. The value of any liver function test is directly proportional to an appreciation of the function or functions it is testing.

3. No *one* test should be considered *the* test of liver function.

4. The proper interpretation of a combination of these tests for specific functions will tell much about hepatic function and the degree of its impairment.

5. Repetition of certain of these tests from time to time in the course of the disease will further tell whether the disease in the liver is progressing, retrogressing, or stationary.

BIBLIOGRAPHY

1. Wallace, G. B., and Diamond, J. S.: The significance of urobilinogen in the urine as a test for liver function, Arch. Int. Med., 1925, xxxv, 698.
2. Muller, F.: Untersuchungen über Icterus, Ztschr. f. klin. Med., 1887, xii, 45. Verhandl. d. Kong. f. inn. Med., 1892, p. 118.

3. Feigl, J., and Querner, E.: Bilirubinämie, Ztschr. f. d. ges. exp. Med., 1919, ix, 53.
4. Barron, E. S. G.: Bilirubinemia, Medicine, 1931, x, 95.
5. Shay, H., Schloss, E. M., and Rhodis, I.: II. The galactose tolerance test in the differential diagnosis of jaundice, Arch. Int. Med., 1931, xlvii, 650.
6. Takata, M.: The colloidal chemical serum diagnosis of pneumonia, Trans. 6 Congr. Far East Assoc. Trop. Med., Tokyo, 1925, i, 693.
7. Takata, M., and Ara, K.: A new colloid chemical fluid reaction, Trans. 6 Congr. Far East Assoc. Trop. Med., Tokyo, 1925, i, 667.
8. Staub, H.: Ueber funktionelle Leberdiagnostik, Schweiz. med. Wchnschr., 1929, lix, 308.
9. Jezler, A.: Die Takat'sche Kolloidreaktion in Serum and Körpeflüssigkeiten und ihre Beziehungen zu Störungen des Eiweissstoffwechsels der Leber, Ztschr. f. klin. Med., 1930, cxiv, 739.
10. Abel, J. J., and Rowntree, L. G.: On the pharmacological action of some phthaleins and their derivates with especial reference to their behavior as purgatives, Jr. Pharm. and Exper. Therap., 1909, i, 231.
11. Whipple, G. H., Mason, V. R., and Peightal, T. C.: Tests for hepatic function and disease under experimental conditions, Bull. Johns Hopkins Hosp., 1913, xxiv, 207.
12. Rosenthal, S. M.: An improved method for using phenoltetrachlorphthalein as a liver function test, Jr. Pharm. and Exper. Therap., 1922, xix, 385.
13. Rosenthal, S. M., and White, E. C.: Studies in hepatic function. VI. A. The pharmacological behavior of certain phthalein dyes, Jr. Pharm. and Exper. Therap., 1924–1925, xxiv, 265.
14. Wintrobe, M. M., and Shumacker, H. S., Jr.: The occurrence of macrocytic anemia in association with disorder of the liver, Bull. Johns Hopkins Hosp., 1933, lii, 387.

CLINICAL USE OF NEW TYPES OF MODIFIED PROTAMINE ZINC INSULIN *

By Renato Sanz del Fierro, M.D.† and Elmer L. Sevringhaus, M.D., F.A.C.P., *Madison, Wisconsin*

The report by MacBryde and Roberts [1] concerning the clinical use of a new type of modified protamine zinc insulin in the treatment of diabetic patients with excellent results moved us to use it in clinical trial in a small number of selected cases.

It is well known that for the great majority of diabetics, crystalline zinc insulin if divided in proper doses, or commercial protamine zinc insulin (PZI) with convenient shifts of carbohydrate allotments in the diet, will suffice. There are, however, a certain number of patients that cannot be controlled by this means, especially when they require large doses of PZI. Liberation of insulin from PZI is essentially steady during 24 hours and its effect lasting more than one day does not keep pace with the needs in these cases. PZI lacks elasticity to prevent post-prandial hyperglycemia with consequent glycosuria and nocturnal hypoglycemia with danger and inconvenience of insulin shock. Treatment of these cases with combined use of crystalline and protamine insulins did not easily overcome the difficulties. It has been also well established that PZI has an excess of protamine sufficient to precipitate almost entirely the regular insulin in the types of mixture most commonly used. This precipitation effect is especially marked because the pH of such mixtures is always below the iso-electric point of insulin, usually between 4 and 5.

Thus, it was a great therapeutic advance when both types of insulin could be combined in a relatively stable form with adjusted pH, the rapidly acting component of such a combination being measured by assay of the supernatant fluid, after centrifugation of the mixture.[2] This is the type of insulin modification we have used in 16 cases at the Outpatient Clinic of the Wisconsin General Hospital. Selection of the cases from among those consulting at our Outpatient Department was made, bearing in mind that it is precisely here that a trial of clinical usefulness could be better made, although we realize that control and follow-up studies cannot be as complete as in hospitalized patients. As a matter of fact, in a ward patient the constants are first, diet; second, activity; and third, environmental condition. The only variable is insulin, its type and dose. The first three conditions cannot be kept as constant in an ambulatory patient and perhaps it is more accurate to assume that all the factors are variables, since all these patients are engaged in their normal and constantly changing activities. In all the

* Received for publication September 14, 1944.
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cases the diets used ranged between protein 50 to 70 grams daily, fat 90 to 225 grams daily, and carbohydrates 70 to 150 grams daily. No revision of diet was attempted during the course of this study. The following table shows some pertinent data.

The first 10 cases were using PZI regularly for diabetic control in doses ranging from 35 to 75 units daily with an average of 58 units daily. As they were shifted to modified protamine zinc insulin (MPZI) stated, the average dose decreased to 52 units daily and a better control was obtained, as shown by the blood sugars which were taken usually two hours after the noon meal. Cases 11 and 12 had been treated in another clinic with regular insulin in three divided doses. The MPZI was used to avoid several daily

TABLE I

No.	Dose and Type of Previous Insulin Units	MPZ Insulin (T-1716) Units	Blood Sugar 2 Hours After Meal		Reason for Change	Clinical Results
			Previously	on MPZI		
	PZI					
1	70	66	234	154	Marked nocturnal reactions.	Excellent. Few and mild early morning reactions.
2	70	40	230	160	Low renal threshold for sugar; frequent nocturnal reactions.	Less frequent reactions.
3	60	65	326	258	Pre-prandial reactions; post-prandial glycosuria.	Better control of post-prandial glycosuria.
4	50	35	176	138	Marked nocturnal and pre-prandial reactions.	Less frequent and milder reactions.
5	70	75	200	117	Instability of control; nocturnal reactions.	Still having reactions with faster acting types (T-1842, AP-125).
6	50	52	246	218	Late afternoon reactions.	Not good. Notes recurrence of diabetic characteristics. On AP-125, fast acting type.
7	65	45	262	258	Frequent nocturnal and before breakfast reactions.	Trial on fast acting types (T-1842, AP-125) not successful. Good with MPZI.
8	50	60	330	216	Poor control of post-prandial glycosuria.	Better control.
9	45	35	202	142	Post-prandial glycosuria; slight morning reactions.	No glycosuria. No reactions.
10	75	65	264	222	Frequent pre-prandial and nocturnal reactions.	No reactions in one month.

TABLE I—*Continued*

No.	Dose and Type of Previous Insulin Units	MPZ Insulin (T-1716) Units	Blood Sugar 2 Hours After Meal		Reason for Change	Clinical Results
			Previously	on MPZI		
	Regular					
11	15, 15, 15	50	220	128	To reduce number of daily injections	Excellent. Fasting blood sugar 114, P. C. 110, 128.
12	15, 0, 20	40	230	168	Instability of control.	Fairly steady blood sugar after meals.
	Mixture					
13	3:1 60	55	266	150	Trouble in mixing insulin; poor p.c. control.	Excellent. No reactions.
14	1:1 60	40	250	175	Instability. Low renal threshold.	No reactions. Better control of post-prandial hyperglycemia, regardless of glycosuria.
15	1:1 60	25	164	?	Glycosuria in daytime; nocturnal reactions.	
	Globin					
16	50	35	214	183	Frequent pre-prandial and nocturnal reactions.	No reactions in one month.

injections and the control secured was excellent although no marked decrease in dosage was noted in these cases. Cases 13, 14 and 15 were using self-prepared insulin mixed in the same syringe. The shift to MPZI was warranted because of the inconvenience of mixing two different kinds of insulin and the possibility of error that actually occurred in several cases. The doses of MPZI required in these patients were consistently lower.

Case 16 had been treated before with globin insulin and complained of frequent late afternoon reactions. The change to MPZI was followed by absence of reaction during a month period although the dosage required was much less.

Several other mixtures of faster acting type were tried. These were completely soluble, containing less protamine. They did not prove satisfactory for the types of patient we have studied. The modified protamine zinc having the 3:1 proportionate effect seemed to meet the requirements of most of our moderate to severe diabetics, as predicted and found by MacBryde and Roberts.[1] This was shown by better post-prandial and nocturnal control of glycemia and consequently of glycosuria, and freedom from frequent hypoglycemic reactions. This modified protamine zinc insulin seems to be unit for unit more effective than the other types of insulin, since smaller dosage brings equal or better control. At present we are trying a completely

soluble mixture, containing slightly less protamine than MPZI. Some of the above described patients are finding it as satisfactory as MPZI, whereas in a few its action is a bit too rapid.

Summary

Observations on 16 diabetic patients with long-standing and essentially stable disease convince us that the special modified protamine zinc insulin of MacBryde and Roberts is the best type of protamine insulin for most diabetics who require 40 or more units daily. One patient (No. 6) found the modified insulin relatively inactive and was unwilling to make a further trial since beginning acidosis occurred. This experience was not duplicated on any other occasion. One other patient (not tabulated) felt that an extemporaneous mixture (5:3) was superior to the specially modified insulin. In all other cases the treatment with a single daily injection of MPZ insulin was preferable to any other routine tried.

BIBLIOGRAPHY

1. MacBryde, Cyril M., and Roberts, Harold K.: Modified protamine zinc insulin: an improvement on standard protamine zinc insulin, Jr. Am. Med. Assoc., 1943, cxxii, 1225–1231.
2. Peck, Franklin B.: Approximate insulin content of extemporaneous mixtures of insulin and protamine zinc insulin, Ann. Int. Med., 1943, xviii, 177.

We are grateful to Dr. F. B. Peck of the Eli Lilly & Co. Laboratory for generous supplies of specially modified insulin (coded as T–1716) and for other combinations of protamine and crystalline insulin, as well as globin insulin.

ABDOMINAL MANIFESTATIONS OF RHEUMATIC FEVER: DESCRIPTION OF A RIGHT RECTUS SYNDROME*

By NORMAN REITMAN, M.D., *New Brunswick, New Jersey*

THE abdominal manifestations of rheumatic fever have been known since Andral, in 1839, called attention to the presence of abdominal pain in cases showing other evidences of rheumatic fever. The French, who were the first to study this problem, found signs and symptoms of peritoneal irritation in rheumatic fever, manifested chiefly by attacks of abdominal pain at the onset of rheumatic activity, and found that when the arthritic pains began the abdominal pains stopped and vice versa.

This important association of abdominal pain and rheumatic fever has largely escaped the attention of the internist and the surgeon. Poynton,[1] in 1925, was the first to describe a chronic peritonitis in a fatal case of rheumatic fever with most of the exudate around the liver and spleen. A loud peritoneal friction rub had been heard during life. Poynton felt that no fatal case of rheumatic fever ever had acute rheumatic changes in the appendix. Paul,[2] in 1930, described the autopsy findings in a rheumatic with polyarthritis, pericarditis, pleurisy, endocarditis and pain in the abdomen. This patient was found to have a serofibrinous peritonitis, very similar to the pleural and pericardial lesions, with underlying Aschoff bodies in the liver and spleen. Worms, in 1930, treated two cases of peritoneal syndrome in rheumatic fever with salicylates and found that the pain and physical signs subsided rapidly.

Although attention has been called to the peritoneal reactions in rheumatic fever, no definite work has pointed to the rectus abdominis muscle as the source of the abdominal pain. Within the past few years several cases of abdominal pain were studied by the author who found that the apparent cause was a rectus myositis which appeared as a manifestation of rheumatic activity. Wood and Eliason[3] in a most comprehensive review of this subject were the first to suggest that the abdominal pain might be due to rheumatic abdominal myositis. These authors, in reporting a case of rheumatic peritonitis, in 1931, stated that the cause of the abdominal pain might be due to (1) rheumatic involvement of the abdominal muscles analogous to torticollis, lumbago or "growing pains," (2) abdominal lymphadenitis or inflammation of the lymphoid tissue in the appendix, (3) pain referred from the pleura, pericardium, diaphragm or spine. However, Wood and Eliason, in the final analysis, felt that rheumatic fever produces a true peritonitis. This feeling was based upon the elicitation of a peritoneal friction rub in two cases,

* Received for publication July 26, 1944.
This work was done before the author entered the Military Service.

the finding of subperitoneal edema in two cases at operation and the post-mortem observation of peritonitis in fatal cases of rheumatic fever reported by Paul and Poynton.

In the cases reported below it was felt that the pathologic lesion was localized to the right rectus muscle rather than an intra-abdominal source. The reason why the right rectus muscle was involved rather than both sides is not clear, unless it be due to the fact that people with pain in the right side of the abdomen are more likely to consult a physician because of the well known location of pain in appendicitis.

Case Reports

Case 1. Mrs. B. K., a 50 year old housewife, was seen in November 1939, in consultation with Dr. S. Z. Neiman. The patient had been ill for 24 hours with abdominal pain and fever. There was no nausea or vomiting. The patient had had chorea in childhood but there was no history of rheumatic heart disease.

Examination revealed marked spasticity in the right lower quadrant with moderate tenderness over McBurney's point. There was no rebound tenderness. The heart was of normal size. The first apical sound was roughened and impure. In the left lateral recumbent position a definite, presystolic, rumbling murmur of mitral stenosis was heard. The temperature was 101° F., pulse 104, respirations 25, and blood pressure 140 mm. Hg systolic and 82 mm. diastolic.

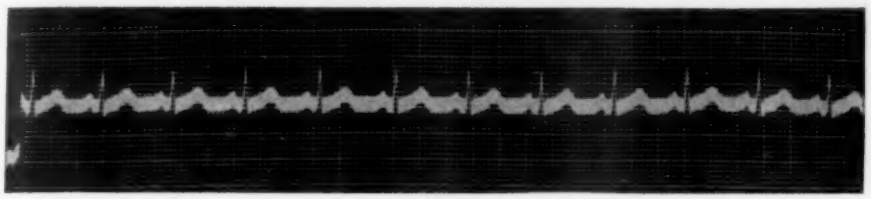
In view of the finding of rheumatic heart disease the sedimentation rate was determined and found to be 50 mm. per hour (Westergren). The white blood cell count was 13,500; polymorphonuclears 72 per cent; lymphocytes 28 per cent. The patient was put on salicylates with a prompt cessation of her pain and temperature in 12 hours. The sedimentation rate remained elevated for three weeks during which time the patient was asymptomatic. This patient subsequently developed auricular fibrillation and moderate congestive heart failure. Her sedimentation rate was not elevated after the original attack. There was no return of abdominal pain.

Case 2. Mrs. L. H., a 21 year old secretary, was first seen in November 1941, because of sharp, sticking, abdominal pain of 24 hours' duration. Pain originated in the right lower quadrant and radiated to the right thigh. No nausea or vomiting was experienced. The patient stated that she had had one or two similar attacks previously.

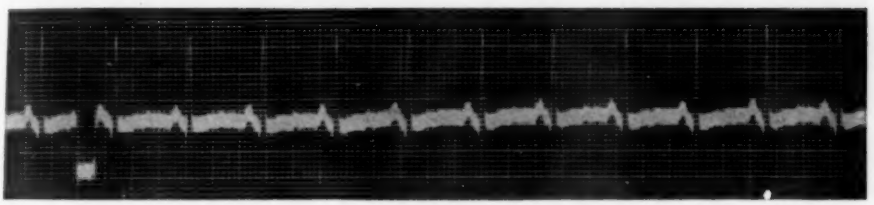
Examination revealed definite tenderness over McBurney's point with marked spasticity in the right lower quadrant. No rebound tenderness was elicited. The white blood cell count was 10,500; polymorphonuclears 63 per cent; lymphocytes 28 per cent; eosinophiles 2 per cent; mononuclears 7 per cent. Nothing else was found on examination. Because of the equivocal blood count the patient was treated conservatively and the symptoms abated in three days. It is interesting to note that the only medication given was aspirin-phenacetin-caffein capsules for the relief of pain.

In March 1942 the patient returned with a similar episode of right lower quadrant pain, tenderness over McBurney's point, no rebound tenderness, nausea or vomiting. The patient had definite tenderness on rectal examination. On splinting the abdomen tenderness was still present. The temperature was 100.2° F., pulse 96, respirations 22. The white blood cell count was 12,900; polymorphonuclears 70 per cent; lymphocytes 25 per cent; mononuclears 5 per cent. Because of the tenderness on rectal examination it was felt that a laparotomy was indicated. At operation an appendix was removed showing no gross or microscopic evidence of disease.

Postoperatively the patient ran a stormy course with fever between 101° and 103° F. and tachycardia. On the third postoperative day she developed a maculopapular eruption on the extensor surfaces of her arms and legs, characteristic of erythema nodosum. The white blood cell count rose to 15,000 with 82 per cent polymorphonuclears and 18 per cent lymphocytes. The abdominal wound was healing well. On the sixth postoperative day the sedimentation rate was found to be



LEAD I



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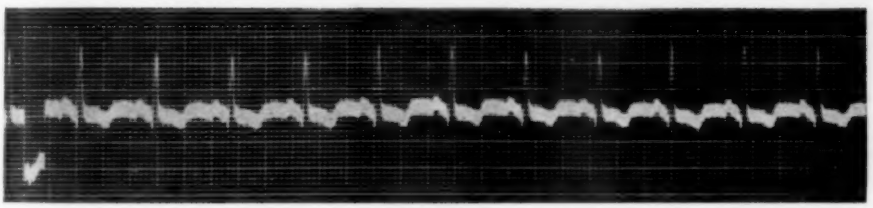


LEAD III

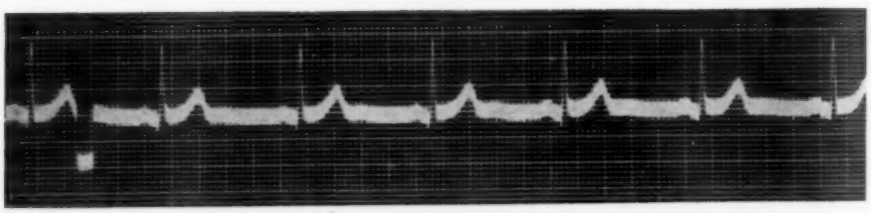
LEAD IV

FIG. 1. Case 2, April 26, 1942.

110 mm. per hour (Westergren). In view of this finding the possibility of acute rheumatic fever with abdominal manifestations was considered and the patient was put on salicylates. Within 24 hours her temperature returned to normal and the pain had disappeared. Tachycardia remained and an electrocardiogram taken at this time revealed inversion of the T-waves in Leads II and III (figure 1), indicating some degree of myocardial change or damage.

The sedimentation rate remained elevated and the erythema nodosum was present for about three weeks. At this time the patient was symptom-free, had a normal pulse, and another electrocardiogram revealed a return of the T-waves in Leads II and III to the normal, upright position (figure 2).

LEAD I



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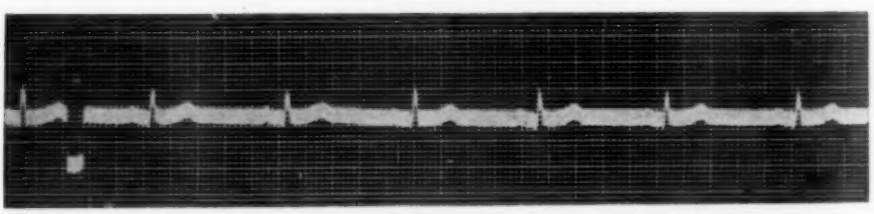

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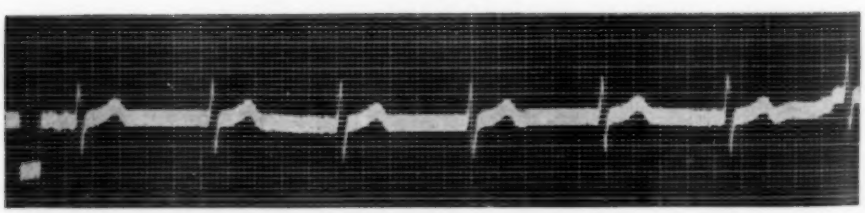

LEAD IV

FIG. 2. Case 2, May 11, 1942.

The patient had a mild return of rheumatic activity with right lower quadrant pain about two months later. Following bed rest and salicylates, her sedimentation rate returned to normal within three weeks. Since then this patient has remained well and no further evidence of rheumatic heart disease has developed.

Case 3. Miss I. S., a 15 year old school girl, was seen in May 1942, complaining of pain in the right side of three days' duration, which was sharp, constant, localized

to the right lower quadrant, and aggravated by walking. The patient was subject to frequent colds and sore throats but had had no known manifestations of rheumatic fever.

On examination the temperature was 99.8° F., pulse 110, respirations 20, blood pressure 114 mm. Hg systolic and 64 mm. diastolic. The abdomen was markedly tender on palpation in the right lower quadrant with the point of maximal tenderness over McBurney's point. No rebound tenderness was found. There was marked spasticity of the muscle in the right lower quadrant. On splinting the abdomen by sitting up without use of her hands, the tenderness remained, thereby localizing the process in the superficial muscles of the abdominal wall.

The heart was found to be enlarged to the left. There were low, rumbling presystolic and loud systolic murmurs at the mitral area; a soft systolic and a loud blowing diastolic murmur was heard at the aortic area. A presystolic thrill could be felt at the cardiac apex but none was present at the base. On fluoroscopy the patient had marked enlargement of the left auricle and left ventricle. Although the patient had definite evidence of mitral stenosis and insufficiency and aortic insufficiency with definite cardiac enlargement, there was no history of diminished cardiac reserve and this was the patient's first knowledge of her damaged heart.

In view of the previous experience the sedimentation rate was determined and found to be 38 mm. per hour (Westergren). The white blood cell count was 15,200, polymorphonuclears 76 per cent, lymphocytes 20 per cent, eosinophiles 4 per cent. There was no shift to the left in the Schilling index. The patient was placed on salicylates with immediate subsidence of the abdominal symptoms. The next day her abdomen was soft and there was only slight generalized abdominal pain. The day following, the patient developed some mild migratory joint pains involving the wrists, ankles and knees, which subsided after three days. Sedimentation rate remained elevated for three and one-half weeks before returning to normal.

The patient's subsequent course was poor as she remained a recurrent and chronic active case of rheumatic fever, developing heart failure, auricular fibrillation and ran a low febrile course for many months, finally dying in March 1944, from congestive heart failure. An autopsy failed to reveal any evidence of peritoneal thickening or appendiceal disease. The patient had cardiac hypertrophy, dilatation of the left ventricle, left auricle, right ventricle, mitral stenosis and insufficiency and aortic insufficiency. Numerous pulmonary infarcts were also found.

Case 4. Miss J. J., an 18 year old colored maid servant, was seen in April 1942, in consultation at the St. Peter's General Hospital, New Brunswick, New Jersey, because of abdominal pain. In this patient the onset of abdominal pain occurred about one week prior to examination. She was seen in the surgical clinic where some right lower quadrant tenderness was elicited. A gastrointestinal series was performed and a report of "a pathological appendix due to non-filling" was made and the patient was admitted for appendectomy.

At the time of the examination a further history was obtained of a severe tonsillitis six weeks prior to admission and the onset of a dull precordial ache with some dyspnea on exertion within the past two weeks. On examination the temperature was 100.4° F., pulse 116, respirations 22, blood pressure 124 mm. Hg systolic and 66 mm. diastolic. The abdomen was definitely tender over McBurney's point but no rebound tenderness was present. There was definite spasticity of the muscles in the right lower quadrant and on splinting the abdomen, as described above, the tenderness persisted. The heart was not enlarged but there was a soft blowing diastolic murmur over the aortic area transmitted to the mitral area. No other murmurs were heard. The blood Wassermann reaction was negative. A diagnosis of rheumatic heart disease with aortic insufficiency was made and the possibility of abdominal myositis due to rheumatic fever was again considered. The sedimentation

rate was 66 mm. per hour (Westergren). The electrocardiogram revealed a P–R interval of 0.24 second. The white blood cell count was 13,300, polymorphonuclears 72 per cent, lymphocytes 22 per cent, mononuclears 6 per cent, eosinophiles 2 per cent.

On salicylates the patient's pain promptly disappeared and within two weeks the P–R interval diminished to 0.14 second. The sedimentation rate remained elevated for six weeks before returning to normal. This patient was followed for one and one-half years and has had no recurrence of rheumatic fever or signs of cardiac decompensation, although the aortic insufficiency has remained.

Discussion

These four cases all presented the difficult differential problem of appendicitis and the question of operation was considered in each. One of the patients (Case 2) had such clearcut signs, including tenderness on rectal examination, that operation was essential. However, all these cases presented signs atypical enough to make one doubt appendicitis and consider other causes for the clinical picture.

In all cases there was an absence of initial cramp-like, generalized abdominal pain, followed by nausea and vomiting, as seen in the majority of cases of acute appendicitis. The initial complaint was severe pain, localized from onset to the right lower quadrant. There was some nausea in Case 2, but no vomiting in any. The discovery of spasticity and marked tenderness over McBurney's point, without rebound tenderness, is the most significant finding on examination. If this symptom were due to appendiceal disease, one would expect a soft abdomen and tenderness early in the course and definite rebound tenderness when the peritoneum became involved and muscle rigidity had developed. These cases were all characterized by the absence of rebound tenderness. Another clinical feature of importance was the persistence of tenderness when the muscle tension of the rectus abdominis muscle was increased by having the patient raise the neck or attempt to sit up without the use of the hands. In all cases the tenderness persisted when this maneuver was performed. If the signs were due to an intra-abdominal pathologic lesion this protective splinting of the intra-abdominal organs would cause a disappearance of the tenderness. Therefore, it is believed that the signs and symptoms were due to an acute rheumatic myositis of the muscles of the abdominal wall rather than to an intra-abdominal lesion.

Another outstanding feature differentiating these cases from appendicitis was the relief of symptoms and signs upon the administration of salicylates in therapeutic doses. This persisted even though low grade fever and other manifestations of a general reaction continued.

The elevated sedimentation rate was the important differential laboratory procedure. In appendicitis a normal sedimentation rate is present unless suppuration with gangrene has occurred. Such a patient is usually sicker than our patients appeared to be. The white blood cell count is also of help. In acute appendicitis one usually finds a leukocytosis with a polynucleosis

and a shift to the left. In our cases of rheumatic abdominal myositis there was a mild leukocytosis but the differential count remained normal.

The evidence of rheumatic fever elsewhere in the body—heart, skin, joints, etc.—in the presence of atypical signs of appendicitis, should always make one wary. Geptill,[4] in discussing the differential diagnosis of the abdominal manifestations of rheumatic fever from acute appendicitis, shares the same opinion. He found eight cases of pseudoappendiceal syndrome in 160 cases of rheumatic fever. He also noted the relative absence of vomiting in abdominal rheumatic fever and its presence in 90 per cent of the cases of appendicitis. Rectal tenderness, which was present in Case 2 of our group and was one of the deciding factors in favor of surgery, also occurred in a few of Geptill's cases, the cause of which is unexplained. He also noted the absence of a shift to the left in the Schilling index. A preceding history of sore throat was found in 30 to 40 per cent of the rheumatic cases and was absent in appendicitis.

In general when a young patient with a previous rheumatic history or signs of rheumatic valvular damage presents himself because of abdominal pain, which is in the right lower quadrant, without any nausea or vomiting, having right rectus spasm with tenderness over McBurney's point, no rebound tenderness, and running a moderate fever; one must seriously consider an abdominal form of rheumatic fever, most likely due to myositis of the rectus abdominis muscle. This possibility should be further substantiated by an elevated sedimentation rate, leukocytosis with a normal Schilling count and rapid subsidence of the abdominal picture under salicylate therapy even when the general reaction continues. The presence of a preceding diarrhea and alternation of abdominal and joint phenomena are striking findings reported among the cases in the literature.

Recently Babbage, McLaughlin and Fruin,[5] of the U. S. Navy Medical Corps, have reported a series of 141 cases of right rectus muscle strain with a clinical picture suggesting acute appendicitis. These cases occurred in healthy navy recruits undergoing their basic training, where they were subjected to severe physical exercise. They note the localization of pain immediately to the right lower quadrant over the rectus muscle and find that the tenderness and pain are aggravated by increasing the muscle tension by raising the head and shoulders from the bed without the aid of the arms. Marked spasm of the rectus muscle was also noted. These findings, definitely due to local disease in the rectus muscle, are identical to observations made by the author, thereby suggesting the superficial origin of the signs and symptoms in the cases reported above.

Babbage, McLaughlin and Fruin used procaine injection of the rectus muscle as a differential diagnostic test in doubtful cases, finding an elimination of pain and spasm in a rectus strain and no effect in appendicitis. This suggests the possible use of this procedure in cases of abdominal rheumatic fever with rectus abdominis myositis and will be tried in future cases.

Summary and Conclusions

1. Four cases of abdominal pain as a manifestation of acute rheumatic fever have been presented. From the observations made, it seems that the origin of the pain is a myositis of the rectus abdominis muscle.

2. The outstanding features are sudden onset of sharp pain in the right lower quadrant without radiation, no nausea or vomiting, marked muscle spasm with tenderness over McBurney's point and absence of rebound tenderness.

3. When such symptoms and signs are found in a patient with a previous rheumatic history the possibility of rheumatic rectus abdominis myositis must be considered.

4. An elevated sedimentation rate and a leukocytosis with a normal Schilling index is a further evidence of the rheumatic origin of the symptoms.

5. A therapeutic test with salicylates will cause subsidence within 12 to 24 hours even though other manifestations of rheumatic fever persist.

BIBLIOGRAPHY

1. Poynton, F. J.: Osler's Modern Medicine (McCrea), Third Edition, 1925, Lea & Febiger, Philadelphia, ii, 187.
2. Graham, R. S., and Paul, J. R.: Studies in rheumatic fever: I. A brief review of clinical and gross pathological findings in eighteen fatal cases, Bull. Ayre Clinical Laboratory, 1926, x, 44.
3. Wood, F. C., and Eliason, E. C.: Rheumatic peritonitis, Am. Jr. Med. Sci., 1931, clxxxi, 482–494.
4. Geptill, P.: Differential diagnosis of abdominal manifestations of acute rheumatic fever from acute appendicitis, Ann. Surg., 1934, xcix, 650–660.
5. Babbage, D. E., McLaughlin, C. W., Jr., and Fruin, I. L.: Strain of right rectus muscle simulating acute appendicitis, War Med., 1944, v, 280–283.

ANOREXIA NERVOSA: THE DIAGNOSIS AND TREATMENT OF INANITION RESULTING FROM FUNCTIONAL DISORDERS*

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IT is interesting that Gull, who first recognized anorexia nervosa as being a condition resulting from starvation, should have also discovered the cause of myxedema, a disease which bears his name. He has been appraised by the English as being one of the most brilliant clinicians of all times. His diagnostic acumen, ability of keen observation and unquestioned curiosity must have been enviable, particularly at a time when laboratory assistance and other aids to diagnosis were far inferior to those which we have at our disposal at the present time. The study of anorexia nervosa has in certain respects been much like the study of myxedema. Both conditions are in most instances completely reversible. Unmistakable physiologic changes occur during the development as well as during the recovery in each instance and in spite of these extensive changes in physiologic processes, significant laboratory findings, with the exception of a low basal metabolic rate common to both, are few. What we know about these conditions has been learned almost entirely from observation, careful inquiry into the medical history and an active sense of curiosity.

In 1930 the writer [1] presented an analysis of a series of cases of anorexia nervosa in which the patients had been seen at the Mayo Clinic from 1917 to 1930 inclusive. The following report is based on additional experience with patients with anorexia nervosa who have been observed at the clinic since that time.

SYMPTOMS AND DIAGNOSIS

The symptoms and findings in any one case of marked inanition as a result of starvation from functional disturbances are good examples of those of any other case in this group. Consequently, the clinical picture constitutes a clinical entity as satisfactorily as any other clinical entity with which we may be considerably more familiar. Anorexia nervosa occurs in young men; however, in such comparative infrequency that for reasons of facility in presentation they are not specifically referred to in this paper.

Clinically the degree of functional anorexia or vomiting extends from instances in which these symptoms are so mild as to have no further unfavorable result than to cause the person to maintain his weight considerably below his normal weight and appear thin, to instances in which these symptoms are so severe that the starvation results in extensive inanition and cachexia. Consequently, the margin between making a diagnosis of anorexia

* Received for publication November 25, 1944.

nervosa and making one of underweight or undernourishment is rather wide and depends on the physician making such a diagnosis. No limiting criteria have been established to distinguish between these two degrees of undernourishment. Rather than to use the term "anorexia nervosa" to designate the entire group of patients presenting inanition as a result of functional disorders it might seem advisable to use such terms as "functional anorexia" or "functional vomiting" with inanition, and to qualify the degree of inanition present by giving the percentage of weight loss from the normal.

Inanition secondary to functional disturbances is due to functional vomiting or functional anorexia, or to a combination of the two, which results in an inadequate caloric intake. The time required for the development of the inanition and the extent to which the inanition may reach depend on the degree of inadequacy of the caloric intake.

In general, patients presenting vomiting alone usually seek medical consultation comparatively early. A diagnosis of functional vomiting is usually made before an appreciable degree of inanition has occurred. However, when vomiting has persisted and is associated with anorexia and a marked degree of inanition, the treatment becomes much more difficult. The vomiting must be overcome before a successful increase of the caloric intake can be brought about. There is no difference in the eventual outcome for the patient who refuses to eat and the patient who does eat but vomits immediately afterward. Patients who vomit an hour or more after meals may do so without vomiting enough food to cause much loss of weight. In such instances weight is lost very slowly and over a long period.

In most of the cases in which marked inanition develops, it does so primarily because of functional anorexia. Although there may be some infrequent vomiting, the vomiting plays only an insignificant rôle in the development of the inanition. As a general rule these patients keep the bulk of their diet below that amount which gives them distress and results in vomiting; consequently, vomiting is not as frequent nor as serious a symptom as anorexia.

I have roughly estimated the daily caloric intake of a number of these patients who had reached a marked degree of inanition and whose weights varied between 55 and 75 pounds (25 and 34 kg.) to be between 900 and 1,300 calories. This low body weight had been stationary for some time.

The symptoms of anorexia nervosa may be divided into two groups: the psychic and the somatic. Briefly, the psychic symptoms resemble the emotional reactions of the spoiled child: loss of morale; loss of pride as evidenced by subterfuges, unsound excuses and explanations regarding symptoms; apathy; reticence; paucity of ideas and negativistic tendencies. Patients suffering from anorexia nervosa may be very tiring in conversation, lack spontaneity, and offer only answers to questions, the answers usually being incomplete. They are difficult to reason with and display mental fatigue. In spite of the large number of psychoneurotic complaints, they

do not express concern over their loss of weight or cachectic appearance. They evade a discussion of the true situation. This in general is a description of the psychic symptoms of the group as a whole; however, it pertains particularly to the younger group of patients. Although the older group beginning at about 26 years of age have tendencies toward the same reactions, they may show them to a lesser degree. However, it must be remembered that these reactions are the result of the effect of starvation on the individual's mental make-up. Consequently, the degree of these reactions will vary with the strength of that individual's mental make-up. Infrequently, the strength of personality may be maintained to such a degree that this alone may in certain instances have the tendency to lead one astray in making a correct diagnosis.

The somatic symptoms consist of evidence of marked loss of weight with the appearance of age, pallor without anemia, in some instances hairiness of the arms and legs, dryness of the hair and skin, intolerance to cold with cold hands and feet, low blood pressure and a slow pulse rate. More than half of the female patients suffering from anorexia nervosa give a history of amenorrhea. The finding of an atrophic type of uterus is common, particularly in young nulliparous women when inanition is marked. The patients complain of various indefinite gastrointestinal disturbances, the most consistent being constipation. In spite of unmistakable evidence of dietary incompetence, there is a lack of recognizable avitaminosis. There may be edema of the ankles, which in most instances is slight. Sighing dyspnea is a frequent occurrence. No particular evidence of caries of the teeth described elsewhere has been observed in patients seen in the clinic. The symptoms and findings of inanition or anorexia nervosa could be more aptly referred to as the depressant effects of starvation.

As to the classification of these patients in regard to age one might logically assume that the condition might occur in more or less equal proportions at all ages. However, clinically this is not the case and I believe that there are logical and sound psychologic reasons why this does not happen. Although the direction of reaction as a result of starvation at all ages is much the same, yet these reactions are tempered and varied in degree by the effects of age.

Functional anorexia and functional vomiting are very common occurrences following psychic disturbances among children up to the age of 12 to 14 years. As a general rule, however, certain temporary situations responsible for the nervous disturbance are corrected long before any marked demonstrable physical changes as a result of starvation have appeared. The mental immaturity, susceptibility to suggestion and trusting tendencies of children make the treatment of anorexia and vomiting due to functional disorders much more approachable than the treatment of the same condition among patients of 14 and 15 years of age and older. Consequently,

it is a very rare occurrence for a child * to go on to a condition of marked inanition and cachexia as a result of starvation due to functional anorexia or vomiting.

During puberty and thereafter, however, the formation of individual ideas and the feeling of independence make the situation much more difficult to handle. Few parents have escaped at least in some degree the worries and problems associated with the battle of adolescence. At these ages romance, the excitable effects of menstruation and the feeling of independence are at a high level. Their desire for recognition of this independence makes this group particularly susceptible to resentment of parental advice and curtailment of their need to assume the privileges of adult life. The magnitude of these desires is common knowledge. Consequently, the adolescent group is surrounded by factors which make them particularly susceptible to psychic disturbances and their ability to make mountains out of mole hills may explain why they are capable of carrying those factors responsible for marked inanition and cachexia to such extremes. In the great majority of cases of anorexia nervosa, while the peak of the weight loss and the full blown picture of inanition may occur several years later, the condition has its origin during puberty or during the few adolescent years following. A small group may have the occurrence of the psychic upset during the third decade; however, as the decade progresses the comparative frequency of cases becomes progressively less.

In the adolescent group the basis for the psychic upset is frequently found to be in the parent. This does not necessarily mean, however, that the parent is dominating or unreasonable, but depends on the degree of the child's resentment to regimentation and the degree of insistence on the part of the parent. The parent is not necessarily responsible for the psychic upset, as the disturbing factor may originate in school, a teacher or in disappointments far removed from the parents and home life. Nevertheless, in this age group there is invariably a psychic upset present although the psychic upset itself or the degree of its effect may not be admitted or in some instances possibly not appreciated by the patient himself.

There is a subgroup of the group of adolescents which I believe deserves brief mention. This subgroup consists of young girls, 13 to 15 years of age, who during the grade school years are somewhat overweight. When they reach the first year of high school they may realize that they are overweight or they may be cruelly reminded of this fact by others. As a result they markedly cut down on their food intake so as to reach the desirable appearance as quickly as possible. However, when they have become satisfied with the amount of weight lost they find that it is impossible for them to eat the amount sufficient to maintain their weight at the level desired. Conse-

* When anorexia nervosa associated with marked inanition occurs before the age of 10 years and persists continuously through adolescence and the years of completion of growth, definite evidence of retardation of skeletal development as well as of development of sexual characteristics occurs.

quently, loss of weight continues to progress to a point at which the symptoms so typical of inanition appear. In this instance then the anorexia, inability to partake of a normal caloric intake in three meals a day and vomiting follow rather than precede the development of inanition. Further remarks will be made in regard to this.

The group of patients more than 30 years of age comprise a much smaller portion of the entire group than those less than 30. The condition of the younger members of this group may be identical with that of those patients under the age of 30 and be secondary to a definite psychic upset. However, after 30 years of age the frequency of the condition decreases and the clinical picture becomes less and less characteristic. In general, the inanition does not have the tendency to reach marked degrees of cachexia and these patients frequently pass unnoticed except for the fact that they are considerably underweight. The older the patient, the less chance one has in assisting him to return to his normal weight. This probably is due to the presence of fixed ideas and inability to coöperate. The older the patient, the more attention one must give to exclusion of organic disease. There is one group of patients in which the sequence of events follows much the same course as that seen in the younger group. This includes older patients who after the extraction of all teeth either have faulty dentures or do not use dentures.

In many of the cases in which a diagnosis of anorexia nervosa was made at the clinic, diagnoses of disturbances of various glands of internal secretion had been made previously and the patients had been treated with injections of glandular preparations without results. Because of the complexity of the clinical syndrome associated with inanition resulting from functional starvation there is little difficulty in understanding why one who is not familiar with this clinical picture tends to attribute its origin to a disturbance of the glands of internal secretion. In other cases diagnoses of vitamin deficiencies had been made and the patients had been treated with intravenously administered vitamins as well as vitamins by mouth. In still other cases diagnoses of Simmonds' cachexia or of other diseases which had been suggested by the presence of the amenorrhea had been made.

In some instances anorexia nervosa had been suspected but this diagnosis had been discarded because the patient was felt not to respond favorably to an increase of food intake. It must be remembered that a daily caloric intake well above the calculated daily caloric requirement for that particular patient must be maintained for several months before the patient regains his normal weight. This probably does not occur in most instances until the end of a six month period. Also it should be kept in mind that in certain instances during an increased caloric intake there may at first be a satisfactory initial gain of weight which may occur for a week or even 10 days and be followed by another week or 10 days during which time little or no weight is gained. However, after this period the patient, without any increase of caloric intake, will begin to gain again. The initial gain of

weight may be explained by an early retention of electrolytes and water. During the period in which no gain of weight occurs, the excretion of water may be balanced roughly by an actual storage of flesh, which may be fat or muscle or both. From that time on, a constant gain of weight occurs. I believe that this period during which no gain of weight occurs has been responsible for the lack of faith in a diagnosis of anorexia nervosa in a number of instances.

I do not believe that Simmonds' disease or other diseases of the pituitary gland need to be considered very often in the differential diagnosis although by others this has been considered a necessity. I am assuming that the term "Simmonds' cachexia" designates a condition of marked inanition and cachexia secondary to atrophy or a destructive lesion of the anterior lobe of the pituitary gland. In this connection it is important to bear in mind that, as Sheehan and Murdoch [2] have pointed out, cases of severe degrees of pituitary necrosis often are not characterized by cachexia. In the experience of the clinic inanition associated with anterior pituitary insufficiency regardless of the cause is the exception rather than the rule. In my experience it is much more important in certain instances to exclude regional and terminal jejuno-ileitis, as a number of patients suffering from this condition have lacked some of the characteristic symptoms of that disease and their symptoms have closely simulated those of anorexia nervosa.

The value of laboratory tests in assisting one to make the diagnosis is limited. There is a lowered rate of metabolism, the degree depending on the length of time the inanition has existed, the degree of the inanition and the normal rate of metabolism of the individual prior to the onset of the inanition. There is a tendency to a depression of the values of the gastric acids, a finding of low blood sugar and a flat glucose tolerance curve. In some cases low values for urinary 17-ketosteroids have been encountered. Normal diuresis after ingestion of water in the "water test" for Addison's disease often does not occur. Assays of the urine for gonadotropic substance (prolan) show that it is either greatly reduced or absent and, as one might expect, the urinary content of estrogenic material is likewise reduced or absent.

Treatment

In the treatment of anorexia nervosa there are three factors which should be considered to be of primary importance: namely, discussion of the situation with the patient, the bulk of the diet and its caloric content.

A frank explanation of the cause of the inanition, an outline of the treatment to be carried out and the reason why the treatment is to be carried out in the manner to be described should be given to the patient before the treatment is begun. The patient should be reassured that in spite of her aversion to food and the discomfort associated with it the treatment will not cause her any great discomfort. It should be pointed out, however, that it is to be expected that she will experience some distress and a sensation of

fullness after meals, both of which before long will gradually become less. It should be explained, also, that this postprandial distress will be only a temporary discomfort but necessary for her to tolerate before reaching a point at which her daily caloric intake will be sufficient to allow her to overcome the condition of inanition. Sufficient time should be given for this discussion so that the patient understands the situation and agrees to cooperate willingly. It is important that these patients receive the minimal degree of sympathy but it is of equal importance that they be not antagonized. If the patient is accompanied by a parent or relative, it is well to have the companion present at the discussion. I have made it a point to see these patients every day for a period of a week or 10 days or until the patient has developed enough confidence to overcome the aversion to food which previously had been the dominating factor militating against her recovery. In the discussion it must be constantly kept in mind that emotional reactions of hysterical type are the primary factors to be overcome in the treatment of anorexia nervosa.

It may be well at this point to digress and point out another factor in the production of some of the symptoms which these patients exhibit. After anorexia or vomiting has existed for a time sufficiently long for signs of inanition to develop, symptoms occur which I believe are entirely secondary to the anorexia and vomiting and do not relate to the inanition per se. By this time in the development of the inanition the patient often experiences epigastric distress and a sensation of overdistention after eating small amounts. The appetite is satisfied and the distress eventually occurs after only a few tablespoonfuls of food. These symptoms persist and as time goes on less and less bulk is tolerated. Finally an actual fear of as well as an aversion to food develops. It seems likely that these symptoms are due to a functional sensory disturbance associated with the stomach itself and are the result of continued lack of bulk in the diet which has been a necessary accompaniment of the period of starvation. If the normal daily moderate distention of the stomach at mealtime plays a rôle in the maintenance of normal psychosomatic appreciation of the food in the stomach, then in anorexia nervosa, because of a continued lack of bulk in the diet, an absence of this mealtime distention of the stomach may well result in an increase of the appreciation of the presence of food in the stomach. As this progresses, even small amounts of food in the stomach may impart a definite and unpleasant sensation of fullness.

An analogous situation is seen in the disturbance of the urinary bladder known as "habit frequency" in which patients cannot tolerate the normal degree of bladder distention. In general, patients will tolerate distention of the urinary bladder to a volume of 300 c.c. without symptoms. Patients, however, who have practiced habit frequency will not tolerate that amount and some of these will tolerate less than half of that amount without experiencing distressing symptoms of vesical distention. Irritability of the urinary bladder in patients having habit frequency is gradually overcome

following an explanation of the situation and advice to decrease the frequency with which the patient voids in spite of the urgency. Rarely, however, it becomes necessary to perform hydrostatic dilatation of the bladder with the patient under anesthesia. For the most part these symptoms of irritability brought on by habit frequency may be analogous to a like effect occurring in the stomach as a result of a continuous absence of bulk in the diet. It seems possible that the alteration of the psychosomatic appreciation of volume occurring in the urinary bladder as a result of habit frequency could similarly occur in the stomach, giving rise to a distressing sensation of distention following the ingestion of small amounts of fluids and solids. The response which occurs in patients suffering from anorexia nervosa to a method of treatment which fundamentally is the same as that given in habit frequency strongly supports this hypothesis.

Vomiting in cases of anorexia nervosa can be regarded as a conditioned reflex, the active stimulus being a sense of fullness which apparently with development occurs at a lower and lower threshold and appears when less and less bulk is present in the stomach. The reversal of this habit is similar to the reversal of the habit frequency of the urinary bladder.

In such an organ as the stomach, which has the properties of contraction and relaxation, I know of no method of measuring volumes for purposes of comparison except in the presence of such conditions as marked dilatation of the stomach due to obstruction at the outlet. For a number of years roentgenologic examinations have been performed on patients suffering from anorexia nervosa, particular attention having been given to the motor function of the stomach, but little of value has been forthcoming from these observations.

Prior to 1938, it had been our custom to serve these patients a high protein diet which consisted of a daily caloric intake of 3,000 calories. At that time an attempt was made to keep the bulk of the diet as low as possible. In some instances, and after the lapse of a period of several months or longer, the results were good. However, in other instances, the patients soon became discouraged because of the associated distress and sensation of fullness. Inability to eat less than half the amount served was very discouraging and as a result, in a number of instances, subterfuges of various kinds were practiced to avoid that distress. To a number of these patients this manner of treatment seemed impossible and they refused to continue with it. Others, however, were able to tolerate the distress and after some time found that they were able to eat everything served to them with a gradual lessening of the distress. This group in general went on to complete recovery. At that time a number of patients whose inanition and anorexia were marked, particularly if vomiting was present, were hospitalized and fairly frequently the treatment was begun by nasal tube feeding. At the present time, however, in spite of marked inanition and anorexia as well as vomiting, it is rarely necessary to hospitalize these patients for nasal tube feeding.

In 1938, we began to treat these patients with particular attention to the

amount of bulk in the diet. Although the caloric value of a high protein diet does not reflect accurately the amount of bulk in the diet, nevertheless, progressively increasing a high protein diet by addition of 300 calories will gradually increase the bulk of the diet. Keeping this in mind, these patients have been treated with the purpose of bringing about a gradually increasing distention of the stomach at mealtime. The treatment has been carried out in the following manner: A rough estimate of the patient's daily caloric intake prior to her arrival at the clinic is made. To this amount is added 300 calories. The patient is served a high protein, high vitamin diet based on that number of calories (usually from 1,300 to 1,500 calories) and is asked to eat everything served to her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. After five or six days the caloric content of the diet is increased by another 300 calories. For the first two or three days discomfort is again experienced; however, the symptoms again become less. This procedure is repeated until the caloric intake is approximately 3,400 or 3,600 calories. These patients experience far less distress eating this diet than they experienced eating the initial diet based on 1,300 to 1,500 calories. Frequently, the distress becomes markedly decreased before the diet based on 3,200 calories has been reached. In a number of instances, the diet has been increased to one based on 3,800 calories or more without difficulty.

At the time of dismissal the patient is instructed in the diet by a dietitian. She is advised to weigh herself two or three times a week. She also is advised that if her gain is not progressive, she can feel sure that without realizing it she has gradually decreased her diet. Because of this tendency I feel it necessary to increase the caloric intake to 3,400 calories or more. The patient is told what her normal weight should be and is advised to continue her diet until her weight reaches a point 5 pounds (2 kg.) greater than her normal weight. Since using this method of treatment the results have been very satisfactory and a number of patients who previously might have been felt to have a unfavorable prognosis have responded surprisingly well and have overcome the inanition.

Orange juice as well as small doses of insulin given 20 minutes before meals for the purpose of stimulating the appetite has been felt by us to be ineffectual and consequently neither has been used as a part of the treatment for a number of years. Also the use of desiccated thyroid as an adjunctive measure was discontinued in 1939. If desiccated thyroid is given in doses sufficient to elevate the basal metabolic rate, this decreases the initial gain of weight. Psychologically, in these cases an initial gain of weight is important.

It appears worth while to report the case of a patient who was recently seen in the clinic and whose difficulties apparently had to do with the problem just presented.

Case Report

A woman 33 years of age came to the clinic on January 26, 1944. She gave a history of having had an eye infection in 1939, which had been diagnosed as being secondary to a general infection. Her weight had been 180 pounds (82 kg.) and her height was 5 feet 6 inches (168 cm.). She had lost her appetite and subsequently had found it impossible to eat more than half of each meal served to her. As a result, during the subsequent two years, her weight had decreased from 180 pounds (82 kg.) to 110 pounds (50 kg.). However, during the summer of 1941, by voluntary forced feedings of more than three meals a day and in spite of postprandial vomiting which had occurred every day or two, she had increased her weight to 140 pounds (64 kg.).

At that time she had experienced an attack of fairly severe epigastric pain associated with vomiting which had been present for part of one day. She had entered a hospital and a complete investigation of the gastrointestinal tract had been made with negative results. She remained in the hospital for a period of 10 weeks, during which time vomiting had occurred frequently as a result of epigastric pain, distress and a sensation of distention which occurred during and after her meals. She had been nervously upset and complained of insomnia and exhaustion. A diagnosis of neurosis was made. After leaving the hospital, during which time her symptoms had persisted, she found her weight to be 102 pounds (46 kg.).

In an attempt to regain her lost weight she began to have six to eight small meals a day consisting of foods primarily of high caloric value. After having followed this procedure for several months she found that her weight had increased to 140 pounds (64 kg.) and that she was feeling very well. However, she also observed that when she tried to restrict her food intake to three meals a day it was impossible for her to maintain her weight. Eating more than a small amount at each meal brought on her old distress and sensation of fullness.

Following examination she was found to be in good physical condition. Roentgenograms of the gall-bladder showed it to be normally functioning and roentgenographic studies of the stomach and colon gave negative results. The results of other laboratory investigations were either negative or within normal limits.

The dietary treatment previously described was carried out. The initial caloric value of the diet was 1,400 calories. The bulk associated with the diet at first caused some distress, which after several days became less. The diet was increased in the manner previously mentioned to 2,600 calories. Because of an increase of weight, the caloric value of the diet was decreased to 2,000 calories, where it was maintained. However, the bulk of the diet was progressively increased. The patient was dismissed from our care on February 17, 1944. At that time she was eating everything served to her and experienced only minor distress and very little discomfort from the sensation of fullness.

Comment. The patient whose case has just been reported is the only one that we have had an opportunity to observe who had regained her normal weight by frequent feedings rather than the customary three meals a day. The recovery from the inanition without overcoming postprandial symptoms is what one would expect as a result of frequent feedings and points out the effect of continued lack of bulk in the diet.

Responses to Treatment

Several different responses common to the group as a whole occurring during treatment have been observed and appear to be worthy of mention. During the first part of treatment breakfast is by far the most difficult

meal with which these patients have to contend. Patients who have dogged resolution to get well may be able to eat the first three meals without unexpected discomfort but have difficulty in eating on the following day. Occasionally, the fourth and fifth meals will result in failure while the following three meals may again not be too difficult. Through persistence on the part of the patient, however, a decrease of the degree, or in some instances disappearance, of postprandial symptoms may occur rather early in the treatment.

Observations made on patients suffering from marked inanition under treatment who have done unusually well from the beginning have within the first two weeks shown unmistakable signs of improvement as evidenced by lessening of postprandial distress, noticeable color to the skin of the face, improvement of attitude, increase of strength and a sensation of warmth. Whether these changes are on the basis of increased food intake or on a psychic basis is difficult to say. However, the sensation of warmth which replaces the constant intolerance to cold, occurs long before elevation of the basal metabolic rate begins and can hardly be completely attributed to the specific dynamic action of protein. The constipation, which in most instances is better described as obstipation, is frequently replaced in a short time by regular bowel movements.

Most patients suffering from marked inanition who respond favorably to treatment will, if closely observed, show edema of the feet and ankles at the end of the first week or 10 days. The edema may not be noticed unless particularly looked for. However, patients who do exceptionally well may have marked edema of the feet and ankles to such extent that they cannot wear shoes. This occurs as a rule during the first two weeks of treatment and concomitantly with the initial gain of weight. The serum protein levels are found to be within normal limits and examinations of the urine as well as tests of renal function give normal results. This edema probably is best explained by the early retention of electrolytes and water which has previously been discussed. As a general rule the edema lasts for a week or two; however, in some instances it lasts longer. Reassurance and general measures usually employed in instances of static edema are advised. It appears that the degree of edema which occurs is in direct proportion to the rapidity of the successive increases of the caloric intake which the patient will tolerate.

The basal metabolic rate is elevated gradually without the administration of desiccated thyroid and appears to return to normal concomitantly with the return of the patient to a normal weight. In one instance the return of the basal metabolic rate followed the return of the patient to normal weight whereas in another the return of the basal metabolic rate preceded the return of the patient to a normal weight.

The function of menstruation is frequently affected in women who have anorexia nervosa. It has been previously mentioned that more than half of the women have amenorrhea. When menstruation persists, although it

may occur with regularity, the amount of flow is diminished. It is well known that a psychic or nervous upset can produce periods of amenorrhea. Inasmuch as this factor has been observed fairly frequently in these cases, this etiologic element must be considered and the fact that amenorrhea or menstrual irregularity fairly frequently antedates loss of weight strongly suggests this. In the patient who has undergone marked loss of weight as a result of inadequate food intake a physiologic reason certainly exists for an inadequate production of gonadotropic principle by the anterior lobe of the hypophysis and for inadequate response on the part of the ovary. Estimations of the amounts of gonadotropic principle in the urine of patients suffering from marked inanition reveal negative results. In cases in which a dietary insufficiency has not existed sufficiently long to bring about marked inanition, there may be evidence of this material in the urine. Examination of the pelves of these women yields results that are rather in proportion to the duration of the amenorrhea. If this has been present for some months, as it fairly frequently is, the mucosa of the vagina is atrophic and vaginal smears reveal a constant state of deficiency of estrogen. Likewise, the uterus will be found to be in various stages of atrophy owing to the long continued and complete lack of stimulation from the ovary. Atrophy of the breasts occurs, although the loss of weight no doubt plays a part in the reduction of their size. In any event, the picture, in so far as the genital tract is concerned, is one of inactivity and atrophy.

The time of onset of the amenorrhea varies greatly. As mentioned previously, amenorrhea may be the first symptom. In other instances it may coincide with the onset of loss of weight, while in still others the inanition may be severe before amenorrhea occurs. In a few cases menstruation may persist in the presence of marked inanition. Perhaps the patient's selection of food has something to do with this. It is conceivable that the woman whose diet contains a relatively large amount of protein might preserve menstrual function longer than one whose chief intake is carbohydrate. However, this occurrence of dietary selection has not been particularly observed by us. When amenorrhea occurs in these patients, the picture becomes one of failure of the pituitary gland to secrete gonadotropins, a failure which is probably due to starvation. The psychic effect in some instances may have helped to initiate the condition but in all probability has little to do with its persistence.

The attitude toward treatment of the amenorrhea in these patients is of importance. Perhaps one could better say that the attitude toward the condition of the genital tract of these women is important. The majority of these patients are young and their reproductive functions are of primary importance to their future. This fact has usually been recognized prior to their coming to the clinic and because of the obvious inactivity of the anterior lobe of the pituitary gland many of them have received injections of extrinsic gonadotropins, without benefit in most instances as one might expect. The presence of a lowered rate of metabolism has been recognized

in most instances and thyroid has been administered previously without beneficial effect on the menstrual function.

It must be kept in mind that most of these women or girls have previously been healthy and have experienced menstrual function within the limits of normality and amenorrhea has developed only as the condition of inanition developed. In other words, there had been no previous evidence of malfunction of the glands of internal secretion concerned with the function of menstruation. Evidence of malfunction did not develop until those glands were deprived of a normal internal environment. Consequently, it has seemed that a return to normal nutrition and so to a normal environment for the pituitary, ovary, thyroid and uterus was the logical first step in treatment. As has been indicated previously, the rate of metabolism rises to within normal limits as the patient, as a result of normal food intake, returns to her normal weight. In many instances the menstrual function returns to normal under the same circumstances and without specific treatment. To some patients who are seen after many months of inanition associated with amenorrhea estrogens have been administered cyclically three weeks out of four in doses of 0.5 mg. of diethylstilbestrol by mouth. This has been done to aid in priming the uterus for subsequent return of ovarian function and to shorten the period of marked atrophy often seen in these cases. In a few cases amenorrhea persists after the return of normal weight and nutrition. When this is true, the estrogens are administered cyclically for the foregoing reason and to imitate the rise and fall of levels of estrogen in the body which may act as a stimulation to the production of gonadotropins. In other cases under the same circumstances low voltage roentgen stimulation to the pituitary and ovaries has initiated menstrual function. Extrinsic gonadotropins may be given a trial under similar circumstances.

In conclusion, it might be suggested that in the care of the type of patient just discussed a consideration of starvation as a cause of the condition be not eliminated as too elementary and discarded for a diagnosis more complex, less understandable and far less hopeful.

BIBLIOGRAPHY

1. Berkman, J. M.: Anorexia nervosa, anorexia, inanition, and low basal metabolic rate, Am. Jr. Med. Sci., 1930, clxxx, 411–424.

2. Sheehan, H. L., and Murdoch, Robin: Post-partum necrosis of the anterior pituitary; pathological and clinical aspects, Jr. Obst. and Gynaec. Brit. Emp., 1938, xlv, 456–489.

ELECTROCONVULSIVE SHOCK THERAPY AND CARDIOVASCULAR DISEASE*

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THE deliberate induction of convulsions in the presence of known or suspected cardiovascular disease would seem to be a very hazardous undertaking. However, it has been possible to treat a considerable number of such patients for psychiatric disorders with very little trouble and a low mortality rate. When the convulsion is induced by the application of an electric current to the brain, there is no direct trauma to the cardiovascular system, and one would expect no more trouble than would follow one or two minutes of strenuous exercise. The results in this series of cases would seem to bear this out.

The following study concerns a group of 750 cases treated with electroconvulsive shock therapy at Mercyville Sanitarium. Among this group were 38 cases with known cardiovascular disease. Most of the patients had mental depressions. The psychiatric results did not differ greatly from those reported in numerous papers on the subject. They were in general very good.

In the group were 19 cases with presumptive to positive evidence of coronary artery disease. Five of the cases had definite histories of previous coronary occlusions together with T-wave negativity in Leads I, II or IV of the electrocardiogram. One patient, a woman aged 74, had a complete left bundle branch block. Two patients had prolongations of the PR intervals to 0.24 second and 0.25 second, respectively. The other patients had definite inversions of the T-waves in Leads I, II or IV. All of these patients withstood the electroshock therapy with no untoward manifestations noted.

Five patients who had auricular fibrillation were treated during the presence of this abnormality. One of these patients was a woman aged 51 at the time her treatments were started. She had had known rheumatic heart disease for many years. There had been two previous episodes of decompensation. The patient had a marked involutional psychosis and she was decompensated for the third time on admission to the sanitarium. There was very marked ascites and dependent edema. The patient was digitalized, acidified with potassium nitrate, and given repeated injections of salyrgan. She was very restless and uncoöperative and little progress was made in the attempt to establish compensation. The patient's general physical and mental condition seemed to be getting worse, so in desperation electroshock therapy was started. After a few treatments, the patient became more composed and coöperative and her edema lessened. By the time the patient had had eight treatments she was very much better mentally. However, she

* Received for publication August 25, 1944.

did not maintain the gain, but again became depressed, negativistic and uncoöperative. She was given five more treatments with again an improvement which did not last. She then received treatments intermittently for several months. The patient had a total of 56 convulsions between April 7, 1942 and July 16, 1943. During all of this time the patient also received salyrgan intermittently and her ascites and edema never entirely cleared. However, the patient's mental condition gradually did improve and it was possible to lengthen the interval between treatments. The patient was finally discharged to her home and her physician reported (June 1, 1944) that the patient was now well mentally, but was still receiving her regular salyrgan injections.

The second patient with auricular fibrillation was a woman aged 40 who had rheumatic heart disease and one previous episode of decompensation. She developed decompensation after her tenth treatment. This responded promptly to digitalization and the administration of diuretics and the patient required no further electroshock therapy, as she recovered from her mental disease (schizophrenia-catatonic type).

The third patient with auricular fibrillation was a woman aged 75 with no history of cardiac disease or vascular hypertension. However, she did have generalized arteriosclerosis and moderate cardiac enlargement. She withstood the treatment without incident.

The fourth patient with auricular fibrillation was a woman aged 48 who had had known rheumatic heart disease for several years. Decompensation had not occurred. On January 8, 1943, the patient had had a cerebral embolus with a right hemiplegia. About three months after the vascular accident she had developed a schizophrenic psychosis. On June 24, 1943 she had another embolus which lodged in the left lower leg. Although the patient had marked pain, and temperature and color changes in the foot, collateral circulation was established with the aid of papaverin and an intermittent venous occlusion apparatus. On April 11, 1944, electroshock therapy was instituted. At that time the patient's hemiplegia had improved very little. She had no use of her right hand and was able to use the leg just enough to walk with the support of an attendant. She received a total of 16 electroshock treatments from April 11, 1944 to June 23, 1944. There was no noteworthy change in her physical condition, but mentally she improved and was discharged to her home on July 9, 1944. When last heard from (August, 1944) the patient was in good spirits and adjusting well to her hemiplegia.

The fifth patient with auricular fibrillation was an emaciated woman (height 61¼ inches and weight 62.5 pounds) of 50 years, who had rheumatic heart disease but no episodes of decompensation. She had developed depression, negativism, and aversion to food. She was just about the thinnest person the writer has ever seen. She was fearful and resistive about everything. A diagnosis of probable schizophrenia was made. It seemed ob-

vious that the patient would soon die unless something drastic was done, so she was started on electroshock treatment. By the time she had had four treatments the patient was cheerful, affable and coöperative, and she ate her meals. Two days after the last treatment the patient developed scattered chest râles and a fever of 102° F. She was given sulfamerazine and the temperature became normal, but she continued to have chest pain. Her condition seemed to be good, but seven days after the last treatment the patient suddenly became dyspneic, cyanotic, and in shock, and died in an hour. An electrocardiogram taken a half hour before death showed some increase in the prominence of the S-waves in Lead I, as compared with the pre-treatment record, but it was not definite enough to verify a diagnosis of pulmonary embolism. No autopsy was done, and the exact cause of death remains uncertain.

Treatment was given to nine patients with hypertension, that is, with a systolic blood pressure over 200 mm. of mercury. In no case were any complications encountered during the administration of electroshock therapy. One of the patients was a woman aged 56 with hypertension approaching the malignant phase. The blood pressure on admission was 215 mm. Hg systolic and 120 mm. diastolic. Examination of the ocular fundi revealed marked narrowing of the retinal arteries, many hemorrhages and exudates and slight papilledema. The patient had had a cerebral vascular accident a few months before her admission and there was a coarse tremor and slight hyperreflexia of the right arm. The patient was very depressed, unresponsive and poorly oriented. A provisional diagnosis of psychosis due to cerebral arteriosclerosis was made. The matter was discussed with the patient's husband and a very poor prognosis was given him. However, it was explained to him that the seemingly obvious diagnosis of psychosis due to cerebral arteriosclerosis might be wrong and that the patient might have an independent mental disease, which would respond to convulsive shock therapy. He was anxious that something be done, so with some misgivings the patient was started on shock therapy. She was given a course of eight convulsions. By the time the treatments were finished the patient seemed to be hopelessly confused and unable to answer the most simple questions. However, within three weeks she became oriented, pleasant, cheerful and she recovered good insight. She was discharged recovered from her mental illness on February 14, 1943. Her blood pressure on discharge was 245 mm. Hg systolic and 130 mm. diastolic. The diagnosis of psychosis due to cerebral arteriosclerosis was revised to involutional psychosis melancholy type. The patient's physician reported (June, 1944) that the patient was living and well mentally, but that her hypertension was the same.

Three other patients with previous cerebral vascular accidents were treated with electroshock therapy with no untoward results.

One patient, a woman aged 44 with rheumatic heart disease without decompensation, was treated. She had a harsh presystolic murmur, some cardiac enlargement, and an inverted T-wave in the fourth lead of her

electrocardiogram. She was given 15 electroconvulsive shock treatments with no complications and no noteworthy change in her mental condition (chronic schizophrenia).

Complications

The only complication other than the one death and the development of decompensation mentioned above was the development of auricular fibrillation, which occurred in one case. This patient was a woman aged 70, whose electrocardiogram was normal and who showed no evidence of cardiac disease other than generalized arteriosclerosis before the treatments. This patient developed auricular fibrillation after 12 treatments. She returned for further electroshock therapy after 11 months. At that time the auricular fibrillation had ceased, and it did not recur with the administration of 10 more electroshock treatments.

Conclusions

Electroshock therapy can be given with remarkably little danger in cases of serious organic disease of the cardiovascular system. In a series of 750 patients treated with electroshock therapy, there were 38 cases with positive evidence of previous damage to the cardiovascular system. With one exception all of these patients survived the electroshock treatment with remarkably few ill effects and complications. Nearly all of the cases treated were suffering from severe mental illnesses, which might well have terminated fatally from undernutrition or suicide if shock treatment had not been used.

PRESENT STATUS OF CHEMOTHERAPY IN TUBERCULOSIS *

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The enthusiasm for chemotherapy of clinical tuberculosis which has been expressed by some authors of articles in newspapers and popular magazines is not as yet shared by most physicians who are utilizing these preparations, although it is widely felt that steady progress is being maintained. Premature dissemination of unreliable information to patients and their relatives can do serious harm if it serves to discourage acceptance of effective conventional treatment, including sanatorium care and collapse therapy. It appears presently important to provide in one article, in a widely circulated medical journal, up-to-date, authentic information on chemotherapy of tuberculosis. With one exception,[1] recent articles for medical readers have appeared in journals intended for specialists or in foreign medical journals.

In 1932 Wells [2] summarized the accumulated knowledge of chemotherapy in tuberculosis and was led to the conclusion that none of the many remedies proposed had demonstrated ability to arrest the progress of this disease in man or in experimental animals. He concluded with these prophetic words: "Probably some new success with some other bacterial infection will be needed to stimulate a new attack on the more difficult problem offered by tuberculosis."

Experimental Investigations

The impetus which Wells thought was needed was provided by the discovery of the chemotherapeutic efficacy of sulfonamide compounds against a variety of bacterial infections. Rich and Follis [3] first recorded the fact that sulfanilamide possessed limited but definite ability to retard the rate of development of experimental tuberculosis in guinea pigs. Soon thereafter observations were extended to include sulfapyridine [4] and azosulfamide (prontosil).[5]

The results suggested that other new chemotherapeutic substances should be tested against experimental tuberculosis as they became available. Promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) had been supplied to us early in 1940 by Dr. E. A. Sharp † for clinical trial in pneumococcus and streptococcus infections of the respiratory tract of man and this drug was the first of the sulfone series to be tried against tuberculosis of experimentally infected guinea pigs. The preliminary results [6] were much

* Received for publication November 7, 1944.

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more encouraging than any previously observed with sulfonamides and led to a long series of investigations. It was shown [7] that promin was capable of actually arresting the progress of otherwise uniformly fatal tuberculosis in guinea pigs and that such results could be achieved even when treatment was delayed for six weeks after inoculation. In a subsequent crucial experiment,[8] laparotomy and biopsy of the liver were performed before treatment, permitting actual comparison of the same lesions before and after administration of the drug. This procedure appeared to provide proof that true retrogression, resolution and even apparent healing of lesions resulted after several months of continuous treatment.

It was logical that other sulfone derivatives be synthesized and subjected to similar experiments to determine their therapeutic efficacy against tuberculosis experimentally induced in guinea pigs. A moderate number of such substances has been produced and tested [9, 10, 11] but full reports have been made only on those which have showed promise. Among such promising compounds were disodium formaldehyde sulfoxylate diaminodiphenylsulfone [12, 13] (diasone) and 4,2′-diaminophenyl-5′-thiazolesulfone (promizole).[14]

The experimental observations of the effects of the drugs mentioned in preceding paragraphs have been verified and amplified by several laboratories.[12, 15, 16, 17] It may be concluded, therefore, that several drugs of the sulfone series are effective in combating and arresting experimentally induced visceral tuberculosis of guinea pigs. The recorded results indicate: (1) that life of animals which continue to receive treatment can be prolonged indefinitely; (2) that grossly visible lesions of tuberculosis diminish in size or disappear from the viscera of treated animals and (3) that on histologic examination evidence of healing trends can be observed, including fibrosis, encapsulation and occasionally calcification. These findings are in striking contrast to the progressive, destructive, fatal disease of untreated control animals. It is important to note that tubercle bacilli usually were not completely eradicated and that latent disease remained even after extremely prolonged treatment, being rekindled into activity when treatment was suspended.[15, 18] In this important respect all available chemotherapeutic agents fall distinctly short of the ideal, even in experimental studies.

Clinical Investigations

Promin. Prompt application of experimental findings to the problems of clinical tuberculosis was attempted. In March, 1941 the first volunteer patients received sulfone therapy for pulmonary tuberculosis at the Mineral Springs Sanatorium. It was soon discovered that human beings did not tolerate promin as readily as did guinea pigs and that only a third to a half of patients could comfortably and safely tolerate doses by mouth which were adequate to yield significant concentrations of the drug in the blood. In May 1942, we reported [19] preliminary clinical results before the National

Tuberculosis Association, meeting in Philadelphia. These results were encouraging but by no means convincing, and the studies were not adequately controlled to justify conclusions being drawn. The original series of 36 treated patients was the subject of a second progress report [20] which was likewise only cautiously optimistic. Other investigators [21, 22, 23] noted similar effects and usually left the impression that a safe and practicable chemotherapeutic remedy for tuberculosis had not been developed. Zucker, Pinner and Hyman [24] could detect no therapeutic effect of promin when it was utilized clinically. However, it should be noted that these workers administered the drug intravenously. When given by this route, the drug is metabolized differently than when given orally.

Diasone. An apparent exception to the view that safe, practicable chemotherapy for tuberculosis is still to be sought is expressed in the report of Petter and Prenzlau [25] concerning the clinical application of disodium formaldehyde sulfoxylate diaminodiphenylsulfone (diasone), but no convincing therapeutic effect was observed by one of us (Pfuetze),[26] who used diasone for 15 months under conditions similar to those of Petter and Prenzlau. The appearance of subsequent clinical reports concerning treatment with diasone will be awaited with unusual interest and we propose that judgment concerning the efficacy of diasone be withheld until these are available.

Promizole. Of the effective drugs, promizole first appeared to have unusual clinical interest because of its low toxicity for man.[27] Clinical studies now in progress already indicate that promizole falls distinctly short of the ideal remedy. We already have concluded that it has no dramatic effect comparable to that observed following treatment of acute diseases with sulfonamides.

One patient with renal tuberculosis has taken this drug in large doses for 10 months continuously without tubercle bacilli being eradicated from the urine. Nine other similar patients have taken promizole for renal tuberculosis for shorter periods of time, often with some apparent symptomatic benefit, but without eradication of the bacilli in a single instance. Treatment of these patients is being continued because of palliative effects and with the hope that cumulative benefits may be observed.

Five patients with tuberculous meningitis have received promizole without therapeutic benefit. In the case of meningitis reported by Keith,[28] in which the patient recovered following treatment with promizole, the presence of tuberculosis never was proved and in his report Keith wrote: "It should, however, be pointed out that acceptable proof of a tuberculous infection by the production of the disease in an animal inoculated with spinal fluid from the patient was not established. The evidence of tuberculosis, while clinically convincing, therefore, must be considered merely presumptive."

Two patients with proved miliary tuberculosis have received promizole under our direction. One of these patients received 24 gm. of promizole daily for 16 days. In neither case was there any beneficial effect.

More encouraging results have been obtained in treatment of other forms of extrapulmonary tuberculosis (cutaneous tuberculosis and tuberculid, tuberculous lymphadenitis, tuberculous sinuses, etc.) but conclusions are not warranted at this time.

A controlled study of promizole therapy in pulmonary tuberculosis is now under way with other collaborators, following a scheme previously outlined,[29] but significant results may not be known until more time has elapsed.

In the majority of cases in which promizole is taken in large doses (12 to 16 gm. per day) moderate to severe anorexia and upper abdominal distress develop, especially after three or four weeks of such treatment. If the dose in such cases is reduced to 8 to 10 gm. per day, the distress usually is obviated. Administration by mouth of such dietary supplements as yeast tablets and preparations of liver extract has appeared to ameliorate the gastrointestinal symptoms. Patients with defective renal function, such as frequently accompanies advanced renal tuberculosis, excrete the drug slowly and hence require restriction of dosage and careful, individualized management. No evidence of renal damage produced by promizole has been observed. Adverse effects on the blood rarely are noted except when huge doses are administered (up to 24 gm. per day). In a few cases acquired allergic sensitivity to promizole has developed 10 to 20 days after institution of treatment and toxic erythema has appeared but promptly has faded following cessation of the treatment.

We have encountered no toxic manifestations of critical severity in observation of more than 85 patients treated; approximately 75 per cent of these have received prolonged treatment (30 to 300 days) This is in striking contrast to the toxic effects observed with other sulfone drugs. The lack of toxicity appears to be due, at least in part, to the fact that the drug is conjugated in the human body, forming a soluble compound which is readily excreted. Concentrations of the drug in the blood are usually rather low (1 to 3 mg. per 100 c.c.). In a few instances, higher concentrations (5 to 12 mg. per 100 c.c.) have been achieved as a result either of excessive dosage or of defective renal function. In such cases considerable malaise developed which might be attributed to the drug.

It has been reported previously[14, 30] that promizole produces consistently a diffuse parenchymatous hyperplasia of the thyroid glands of guinea pigs and rats. This goitrogenic effect appears to be similar to that of derivatives of thiourea, sulfocyanates and some other goitrogenic agents. This effect is reversible on discontinuation of administration of the drug. These facts were available to us from the beginning of our clinical observations and hence particular effort has been made to determine if any goitrogenic effect would be exerted on patients who received promizole. Palpation of the thyroid gland, determination of the basal metabolic rate and determination of values for blood cholesterol have shown no physiologic derangement following prolonged administration of this compound.

In the case mentioned in a previous paragraph, in which the patient received 24 gm. of promizole daily for 16 days for treatment of miliary tuberculosis, no hyperplastic changes were found in the thyroid gland at necropsy. On the basis of observations of animals, it would appear that the amount of promizole which this patient received should have been adequate to produce definite hyperplasia of the thyroid gland in susceptible animals.

The Need for Careful Research in Tuberculosis

Clinical studies designed to appraise the therapeutic value of substances for treatment of tuberculosis should be carried out with the same controlled scientific methods which are universally demanded in laboratory studies. In no disease is this more difficult than in tuberculosis and especially in pulmonary tuberculosis. Some criteria for such studies have been outlined [29] and it is hoped that a number of institutions may succeed in carrying out observations on treated patients with constant reference to a comparable control group of patients who do not receive chemotherapy.

Progress in research on tuberculosis has been unavoidably slow and will continue at a slower pace than in the case of acute diseases. This appears inevitable in a disease such as tuberculosis of man, which shows a pronounced tendency to spontaneous healing but which may lie latent for many years. Tuberculosis of guinea pigs and of man are different diseases, even though the etiologic agent is the same, and results appear to demonstrate that clinical predictions cannot be based safely on results obtained with experimental animals. This is due in part to the mechanical handicaps against healing produced by the destructive effects of chronic tuberculosis as it frequently affects tissues and especially the lungs of human beings. Mechanical correction by methods of collapse therapy is not likely to be entirely supplanted in such cases and if an effective chemotherapeutic agent eventually should be developed, its rôle is likely to be that of an adjuvant to conventional methods of treatment.

The urgent need for more rapid methods of forecasting the chemotherapeutic potentialities of new compounds made for use against the tubercle bacillus is obvious.[31] The in vitro approach appears logical but as yet no investigator has described such a method which correlates with results in vivo. Serious lack of correlation has been shown in the case of 2,4′-dichlorobenzophenone.[32, 33] It should also be recalled that many gold compounds are effective in vitro but not in vivo. In some instances the validity of studies made in vitro can be questioned because cultures of rapidly growing strains of avirulent acid-fast bacilli have been employed and their genetic relationship to bacilli of tuberculosis is uncertain. Youmans [34] recently has demonstrated that avirulent and virulent strains of acid-fast bacilli may behave quite differently toward chemotherapeutic substances in vitro. His results suggest that in future efforts to develop in vitro tests, strains of at least standard virulence should be employed. The significance of reports of work in which

cultural methods are employed can be judged only when extensive parallel studies have been carried out with experimentally infected animals.

Summary and Comment

Several drugs of the sulfone series have demonstrated a striking ability to arrest tuberculosis experimentally induced in guinea pigs. The tubercle bacillus must be added to the long list of organisms amenable, at least to some extent, to the chemotherapeutic approach. Three substances, promin, diasone and promizole, have been subjected to clinical trials with mildly encouraging, but not conclusive results. Promizole has the distinct advantage of low toxicity for man but its clinical efficacy has not been adequately demonstrated at this time.

It now appears certain that none of the drugs available for chemotherapy of tuberculosis has any clinical therapeutic effect comparable to the prompt and striking results commonly observed when sulfonamide drugs and penicillin are utilized in treatment of acute diseases. It is not known whether the fact that results with tuberculosis are less striking is due (1) to peculiarities of the tubercle bacillus, (2) to the unusual tissue responses in tuberculosis, or (3) more probably to the limited chemotherapeutic properties of drugs studied thus far.

Appraisal of chemotherapy in clinical tuberculosis must await the performance of adequately controlled clinical studies or the development of a remedy so powerful that results are immediately obvious. If a chemotherapeutic agent of practical application becomes available, its existence should be announced to the medical profession through proper professional channels. In the meantime, physicians should advise their patients to accept conventional forms of treatment, especially sanatorium care and collapse therapy, the value of which has been well established.

BIBLIOGRAPHY

1. Hinshaw, H. C., and Feldman, W. H.: Treatment of experimental tuberculosis; use of sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate ("promin") with notes on some toxic effects observed in man, Jr. Am. Med. Assoc., 1941, cxvii, 1066–1068.
2. Wells, H. G.: Chemotherapy of tuberculosis, Yale Jr. Biol. and Med., 1932, iv, 611–626.
3. Rich, A. R., and Follis, R. H., Jr.: Inhibitory effect of sulfanilamide on development of experimental tuberculosis in guinea pig, Bull. Johns Hopkins Hosp., 1938, lxii, 77–84.
4. Feldman, W. H., and Hinshaw, H. C.: The effect of sulfapyridine on experimental tuberculosis in the guinea-pig, Proc. Staff Meet. Mayo Clin., 1939, xiv, 174–176.
5. Birkhaug, Konrad: Treatment of experimental tuberculosis with sulphonamide, Brit. Med. Jr., 1939, ii, 54–57.
6. Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effect of promin (sodium salt of p,p′-diaminodiphenyl-sulfone-N,N′-dextrose sulfonate) on experimental tuberculosis: a preliminary report, Proc. Staff. Meet. Mayo Clin., 1940, xv, 695–699.

7. Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis; sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate, Am. Rev. Tuberc., 1942, xlv, 303–333.
8. Feldman, W. H., Mann, F. C., and Hinshaw, H. C.: Promin in experimental tuberculosis; observations on tuberculous guinea pigs before and after treatment with sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin), Am. Rev. Tuberc., 1942, xlvi, 187–195.
9. Feldman, W. H., and Hinshaw, H. C.: Comparative effects of six compounds administered with therapeutic intent to tuberculous guinea pigs, Am. Jr. Clin. Path., 1943, xiii, 144–147.
10. Smith, M. I., Emmart, E. W., and Westfall, B. B.: The action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis, Jr. Pharmacol. and Exper. Therap., 1942, lxxiv, 163–174.
11. Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effects on experimental tuberculosis of 4,4′-diaminodiphenylsulfone, Am. Jr. Med. Sci., 1944, ccvii, 290–305.
12. Calloman, F. F. T.: New derivatives of diaminodiphenylsulfone; their therapeutic effect in experimental tuberculosis of guinea pigs, Am. Rev. Tuberc., 1943, xlvii, 97–106.
13. Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Therapeutic effects of disodium formaldehyde sulfoxylate diaminodiphenylsulfone in experimental tuberculosis, Arch. Path., 1943, xxxvi, 64–73.
14. Feldman, W. H., Hinshaw, H. C., and Mann, F. C.: The effects on experimental tuberculosis of 4,2′-diaminophenyl-5′-thiazolesulfone (promizole); a preliminary report, Proc. Staff Meet. Mayo Clin., 1944, xix, 25–33.
15. Medlar, E. M., and Sasano, K. T.: Promin in experimental tuberculosis in the guinea pig, Am. Rev. Tuberc., 1943, xlvii, 618–624.
16. Steenken, W., Jr., Heise, F. H., and Wolinsky, E.: Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin, Am. Rev. Tuberc., 1943, xlviii, 453–460.
17. Armstrong, A. R., Rae, M. V., Lucas, C. C., and Greey, P. H.: Effect of promin on experimental tuberculosis, Am. Rev. Tuberc., 1944, l, 160–162.
18. Feldman, W. H., and Hinshaw, H. C.: Promin in experimental tuberculosis: effects of prolonged treatment with sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin) on subsequent reinfection, Am. Rev. Tuberc., 1945, li, 268–275.
19. Hinshaw, H. C., Pfuetze, K. H., and Feldman, W. H.: Treatment of tuberculosis with promin; a progress report, Am. Rev. Tuberc., 1943, xlvii, 26–34.
20. Hinshaw, H. C., Pfuetze, K. H., and Feldman, W. H.: Chemotherapy of clinical tuberculosis with promin; p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate, a second report of progress, Am. Rev. Tuberc., 1944, l, 52–57.
21. Tytler, W. H., and Lapp, A. D.: Treatment of superficial tuberculous lesions by local application of promin, Brit. Med. Jr., 1942, ii, 748–749.
22. Heaf, F. R. G., Hurford, J. V., Eiser, A., and Franklin, L. M.: Tuberculosis treated with promin, Lancet, 1943, i, 702–704.
23. Dancey, R. J., Schmidt, R. H., Jr., and Wilkie, J. M.: Promin in pulmonary tuberculosis; a progress report, Am. Rev. Tuberc., 1944, xlix, 510–534.
24. Zucker, Gary, Pinner, Max, and Hyman, H. T.: Chemotherapy of tuberculosis: promin by the intravenous drip method, Am. Rev. Tuberc., 1942, xlvi, 277–284.
25. Petter, C. K., and Prenzlau, W. S.: Treatment of tuberculosis with diasone, Am. Rev. Tuberc., 1944, xlix, 308–322.
26. Pfuetze, K. H.: Diasone in treatment of pulmonary tuberculosis, Dis. of Chest (In press):
27. Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H.: The clinical administration of 4,2′-diaminophenyl-5′-thiazolesulfone (promizole) in tuberculosis: a preliminary report, Proc. Staff Meet. Mayo Clin., 1944, xix, 33–36.

28. KEITH, H. M.: Use of chemotherapy in a case of tuberculous meningitis, Proc. Staff Meet. Mayo Clin., 1944, xix, 36–37.
29. HINSHAW, H. C., and FELDMAN, W. H.: Evaluation of chemotherapeutic agents in clinical tuberculosis; a suggested procedure, Am. Rev. Tuberc., 1944, l, 202–213.
30. HIGGINS, G. M., and LARSON, R. A.: Hyperplasia of the thyroid gland induced by 4,2′-diaminophenyl-5′-thiazolesulfone (promizole), Proc. Staff Meet. Mayo Clin., 1944, xix, 137–141.
31. FELDMAN, W. H., and HINSHAW, H. C.: Chemotherapeutic testing in experimental tuberculosis; suggested outline of laboratory procedures for testing anti-tuberculosis substances in experimentally infected animals, Am. Rev. Tuberc. (In press).
32. FREEDLANDER, B. L.: Effect of benzophenone and allied compounds on human tubercle bacilli in vitro, Proc. Soc. Exper. Biol. and Med., 1942, li, 153–156.
33. FELDMAN, W. H., HINSHAW, H. C., and MOSES, H. E.: Comparative effects on experimental tuberculosis of 2,4′-dichlorobenzophenone and 4,4′-diaminodiphenylsulfone, Proc. Soc. Exper. Biol. and Med., 1943, liv, 60–62.
34. YOUMANS, G. P.: Personal communication to the authors.

BRONCHOSPIROMETRY *

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By spirometric examinations the total functions of both lungs can be studied. Bronchospirometry is a relatively recent method by which the functions and volumina of each lung are determined separately at the same time. Jacobaeus, Björkman and Frenckner [12] were the first to publish such studies in 1932. They used a double-channelled metal bronchoscope. A number of studies were done with this method by Björkman [2]; Frenckner and Björkman [6]; Jacobaeus [8, 9]; Bezançon, Braun, Soulas and Cachin [1]; Brighton and Barach [3]; and Jacobaeus and Bruce.[10, 11]

In 1939 Gebauer [7] reported a soft-rubber bronchial catheter, constructed for use in bronchospirometry. Before that publication we had already started to do bronchospirometric studies with a similar catheter which had been devised independently by Zavod.[22] The introduction of this instrument is less disagreeable to the patient than the metal bronchoscope, hence the respiratory mechanism is less disturbed and the results, therefore, are more closely comparable to those obtained by spirometry.

Results of studies with the soft-rubber catheter have been reported by Gebauer [7]; Leiner, Pinner and Zavod [14]; Vaccarezza, Lanari, Bence and Labourt [18, 19]; Pinner, Leiner and Zavod [15]; Whitehead, O'Brien and Tuttle [20]; Wright and Woodruff [21]; Steele [17]; and Leach.[13]

The catheter and the technic of its introduction have been described in detail by Zavod.[22] Complete local anesthesia and sedation are essential.

When the catheter is in place, the proximal openings of the two channels are connected to two spirometers, such as are described by Cournand, Richards and Darling.[5] The ventilation of each lung is then recorded separately and simultaneously.

Figure 1 is a tomogram showing the catheter in correct position, as it is also seen by fluoroscopy. A flexible steel plate in the tip of the catheter and the capillary air leads are radio-opaque.

On the following pages we wish to present a summary of the main results of bronchospirometric studies which were pursued at Montefiore Hospital during the last five and a half years.

Indications and Contraindications for Bronchospirometry

Pulmonary function tests may be compared to renal function tests. In diffuse diseases of both kidneys, such as the various types of Bright's disease, we usually are interested only in the total function of both kidneys and use

* Received for publication June 5, 1944.

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tests by which the total renal function is revealed. Correspondingly we examine the total functions of both lungs by spirometric tests in diffuse bilateral pulmonary disease, such as emphysema and pneumonoconiosis. However in a unilateral or predominantly unilateral renal disease (for instance renal tumor), the functions of each kidney are studied separately. In our opinion, the same should be done in unilateral pulmonary disease, particularly preceding irreversible operations on one lung (thoracoplasty,

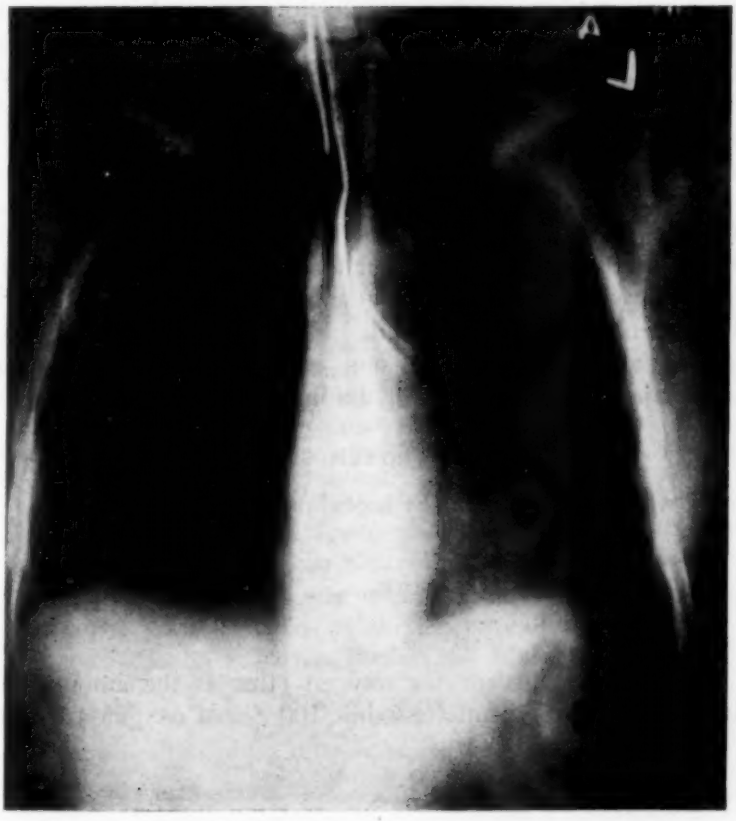


FIG. 1. Tomogram showing the bronchospirometry catheter in correct position. The flexible steel plate in the tip of the catheter as well as the capillary air leads can be seen.

lobectomy, pneumonectomy) if there is any doubt about the efficient function of the other lung. Clinical and roentgenological examinations frequently do not reveal the functional status of one lung.

Besides this practical application, bronchospirometry permits us to study various physiopathological problems of respiration, especially those concerned with the compensatory mechanisms which are called forth in one lung by disease or operative procedures (collapse measures, lobectomy).

Contraindications to bronchospirometry are tuberculous ulcerations of

the larynx and, to a lesser extent, of trachea or bronchi. In addition to that, patients who have high fever, who have had a recent hemoptysis, or who are otherwise very ill should not be subjected to intubation. In patients with large amounts of viscous sputum it is often impossible to obtain satisfactory records because of obstruction of the channels.

We have attempted bronchospirometry about 380 times and have obtained 270 satisfactory records. In no patient have we had a serious accident. One female who had a vital capacity of 770 c.c. (24 per cent of normal) became very dyspneic during induction of the tube; we would, therefore, advise against bronchospirometric studies on patients with severely depressed vital capacity. We saw several slight reactions due to cocaine.

One female patient was so excited that she hyperventilated and got a tetanic attack; trismus developed, the patient pinched the tube with her teeth and nearly choked herself; the tube was removed and the patient recovered immediately. Another female patient had a severe bronchospastic attack after the examination was over; she was relieved by adrenalin. In three patients fever and nonspecific pulmonary infiltrations appeared on the day following bronchospirometry. These infiltrations cleared within a short time and no permanent damage ensued. No spread of the tuberculous process was seen in any case. Many of our patients had two or three bronchospirometric examinations without any untoward effect.

Results of Bronchospirometry

The data which we determine by bronchospirometry for each lung are:

(1) Oxygen intake per minute;
(2) Minute volume of respiration;
(3) Respiratory rate;
(4) Tidal air;
(5) Ventilation equivalent for oxygen (that is the amount of air in liters which a lung ventilates while 100 c.c. of oxygen are absorbed);
(6) Vital capacity;
(7) Reserve air;
(8) Complementary air.

Compared with normal respiration, the respiration through the bronchospirometry tube is modified. The changes are similar to those which are found in the breathing in stenosis. Statistical analyses of such data will be published elsewhere. Here we wish to present only those data which are pertinent for the understanding of our results.

The disturbance in ventilation and respiration caused by the introduction of the bronchial catheter is sufficiently marked to vitiate, within certain limits, the values found by bronchospirometry for pulmonary volumina, oxygen intake and minute volume. All absolute values must, therefore, be determined spirometrically. The bronchospirometric data provide the much

needed information of how the various factors are distributed between right and left lung.

Comparison of Spirometric and Bronchospirometric Findings Where the Latter Give Additional Information

All patients in whom bronchospirometric studies were done had also spirometric examinations. In a certain number of cases only bronchospirometry revealed abnormal functions of one lung whereas the spirometric findings were normal or nearly normal. We will present a few cases out of this group.

87. M. W., a 29 year old male, had a pneumothorax on his right side with 40 per cent collapse. The vital capacity on spirometry was 2,650 c.c. Maximum breathing capacity divided by minute volume was 11.3, a finding which is consistent with a normal respiratory reserve. On bronchospirometry it was found that the oxygen intake of the right lung was only about one third of the total oxygen intake. In spite of a normal respiratory reserve, the right lung contributed only about 30 per cent (instead of 54 per cent under normal conditions) to the total oxygen intake.

149. A. O., a 31 year old female, showed a diffuse infiltrative lesion between the apex and the second anterior rib on the left and minimal infiltrations in the right apex. The vital capacity was 3,600 c.c., or practically normal; the ventilation equivalent, as found by spirometry was 3.4 l. Bronchospirometry revealed that the right lung had a vital capacity of 2,150 c.c., the left lung of 1,390 c.c. The ventilation equivalent of the right lung was 3.5 l, the ventilation equivalent of the left lung was 4.3 l. Bronchospirometry thus revealed definite functional damage to the left lung, whereas the findings on spirometry were practically normal.

The ventilation equivalent is one important index of respiratory efficiency. It is often found that a normal value obscures the fact that the ventilation equivalent of one lung is much increased, indicating impaired function in terms of a disturbed relation between ventilation and available pulmonary circulation. Table 1 (Pinner and Margulis [16]) shows examples

Table I

Comparison of Ventilation Equivalent as Determined by Spirometry and by Bronchospirometry

Patient Number	Spirometry	Bronchospirometry	
		Left Lung	Right Lung
62	2.9	*4.6*	2.1
50	2.4	1.2	*4.7*
151	3.1	*5.1*	1.8
69	2.8	*5.7*	2.7
51	2.6	*6.3*	2.2
171	2.9	1.8	6.3
49	2.7	*6.3*	2.3
56	2.2	*7.4*	2.6
74	2.8	2.1	*8.2*
46	2.2	*10.3*	2.3
69	1.9	*16.4*	2.2

of the striking discrepancy that may exist between the ventilation equivalent, as determined spirometrically for total function and that of single lungs, as estimated bronchospirometrically. A high ventilation equivalent signifies that oxygen resorption is more damaged than ventilation; in such cases the vital capacity may be close to normal, whereas the respiratory function is severely damaged, emphasizing again that vital capacity determination per se is not a measure of respiratory function.

Discrepancies between Roentgenologic and Bronchospirometric Findings

The functions of a lung may be much better or much worse than one might expect from clinical and roentgen-ray findings. Jacobaeus, Frenckner and Björkman [12] pointed out in their first paper that "there is a certain lack of conformity between the results of roentgen examination and those obtained by the bronchospirometric test."

A few cases are presented in which certain bronchospirometric findings were not suspected by roentgenological and clinical observations.

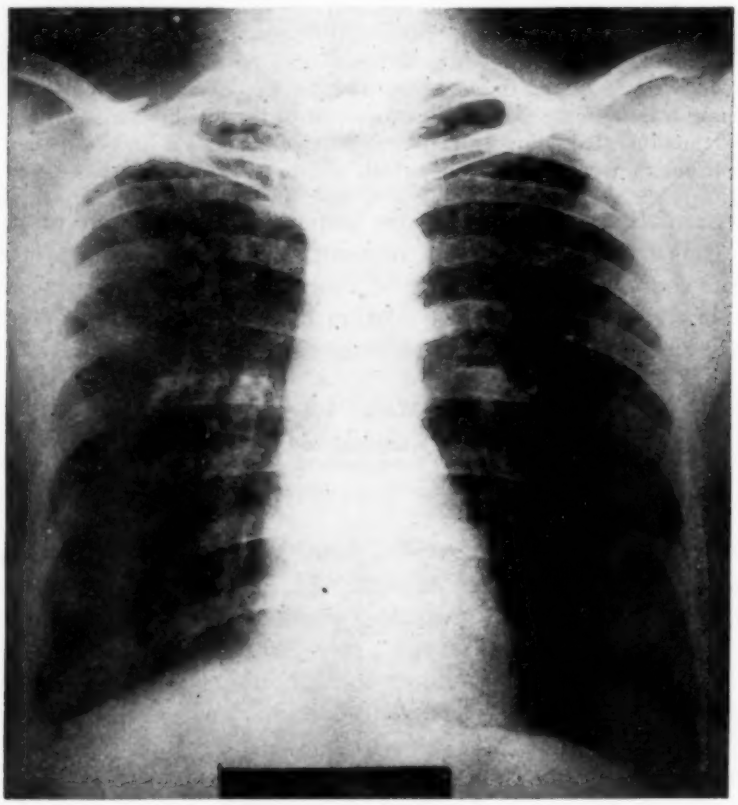


Fig. 2. Chest roentgenogram of patient 72, B. M. Findings for left lung in per cent of total. Oxygen intake: 43; tidal air: 51; vital capacity: 54.

72. B. M. was a 35 year old male. Roentgen-ray examination (figure 2) showed in the right lung moderate fibrosis in the midzone and slight fibrosis of the upper half; the left lung was clear. In spite of the pathological changes in the right lung, the percentage distribution of the pulmonary volumina and the oxygen intake are about normal. The history revealed that the patient had had a pleurisy on the left seven years prior to these studies. As has been shown by Pinner, Leiner and Zavod,[15] pleurisy is often the cause of considerable functional damage of a lung. The right lung here compensated for the damaged left lung.

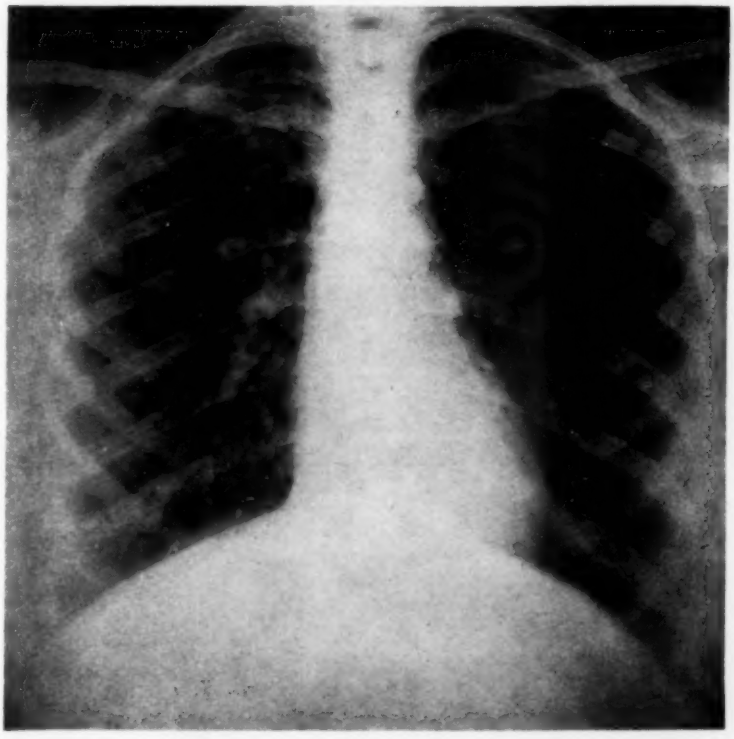
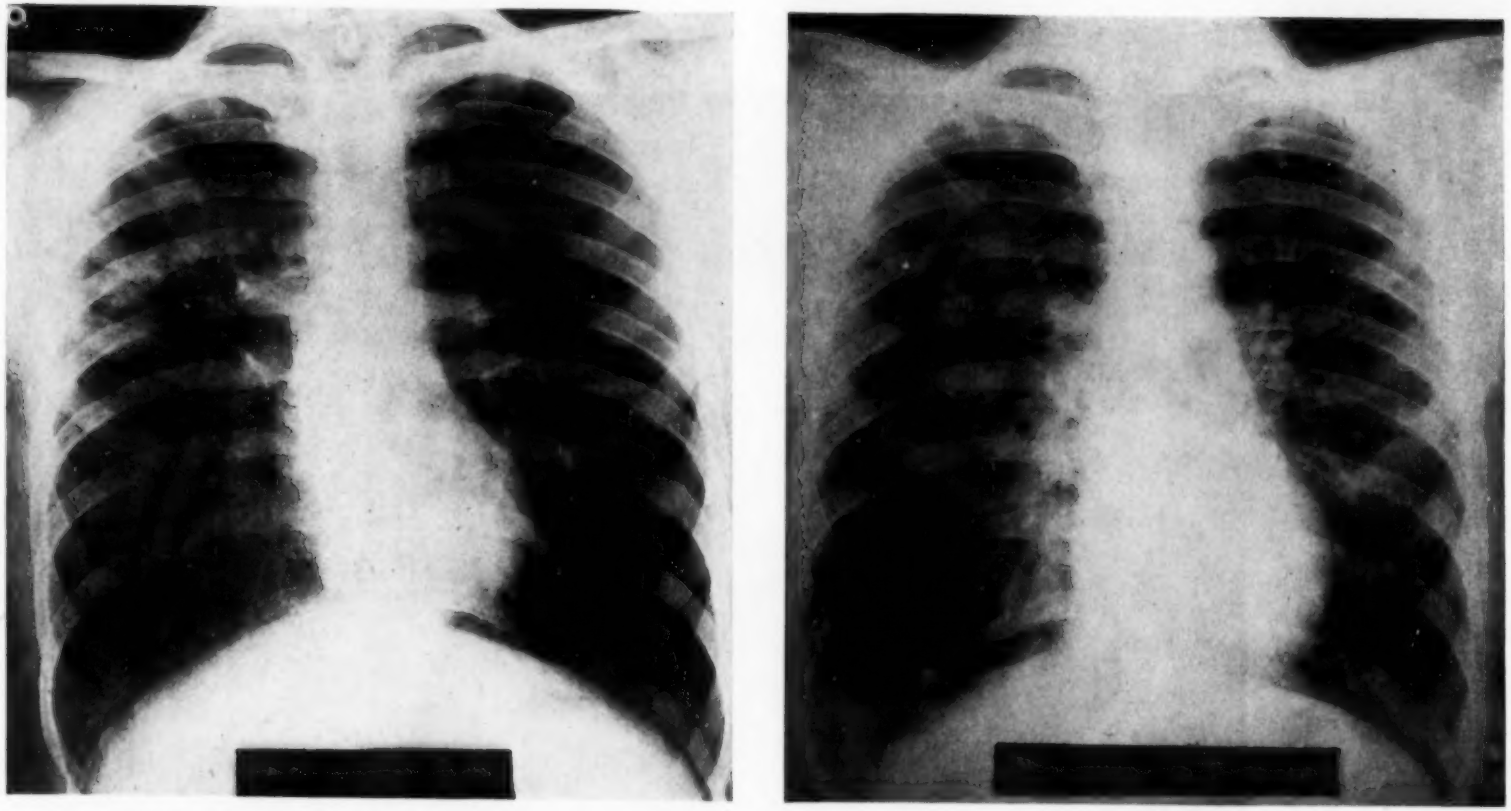


FIG. 3. Chest roentgenogram of patient 150, M. Y. Findings for right lung in per cent of total. Oxgen intake: 58; tidal air: 49; vital capacity: 51.

150. M. Y. was a 22 year old female. In spite of mottled infiltrations on the right from apex to the fourth anterior rib and multiple small cavities (figure 3) there seemed to be no functional damage of the right lung; the distribution of the functions between right and left lung was approximately the same as we would expect if both lungs were normal. This shows that parenchymal lesions frequently do not demonstrably impair pulmonary functions.

264. R. T. was a 23 year old male. The figures (figures 4a and b) given were found before and after induction of pneumothorax. In spite of a reduction of the vital capacity we notice an increase of the oxygen intake on the collapsed side. This might have been caused by reduction of dead space and more efficient utilization of the functioning portions of the lung. This question has been previously discussed (Leiner, Pinner and Zavod [14]).



A B

FIG. 4. Chest roentgenogram of patient 264, R. T., before and following induction of right pneumothorax. Findings before pneumothorax for right lung in per cent of total. Oxygen intake: 29; tidal air: 50; vital capacity: 50. After induction of pneumothorax, oxygen intake: 44; tidal air: 46; vital capacity: 33.

Lungs with Very Poor Functions; Lungs with Strictly Parenchymal Lesions; Reëxpanded Lungs

Theoretically, according to Björkman,[2] the left lung contributes 46 to 47 per cent of the total oxygen intake. In order to find out what the causes of particularly severe functional damage were we selected patients in whom the oxygen intake of one lung was only 25 per cent or less of the total oxygen intake. It was found that each of these patients had pleural involvement: pneumothorax followed by fibrothorax, pleural obliteration, pleuritis. This was often only revealed later when attempts at inducing a pneumothorax were unsuccessful because of pleural obliteration. Three patients in this series had had phrenicectomy. A paralyzed diaphragm apparently contributes considerably to impairment of function (Jacobaeus [8,9]; Cournand and Richards [4]). In contrast, many lungs with active parenchymal lesions without pleural involvement show relatively little functional damage even if the parenchymal lesions are extensive. It is of great practical importance that pleural involvement which cannot always be diagnosed by roentgenologic examination may lead to more severe functional damage than do much more obvious parenchymal lesions.

Effect of Collapse Therapy on Pulmonary Function

Pneumothorax. We studied 18 patients before and several months after the induction of unilateral pneumothorax. The average functional changes in the collapsed and contralateral lungs were as follows: In the collapsed lung there was an average decrease of 35 per cent of oxygen intake; the minute volume decreased nearly 20 per cent (note that oxygen intake drops relatively more than minute volume!); the vital capacity was reduced by 45 per cent, the reserve air by 63 per cent, the complementary air by 45 per cent, the tidal air by 17 per cent; the ventilation equivalent rose by 27 per cent from 2.9 l to 3.7 l.

In the contralateral lung, the oxygen intake rose 30 per cent, the minute volume 16 per cent; the vital capacity, reserve air and complementary air dropped less than 10 per cent. The tidal air rose by 20 per cent and the ventilation equivalent decreased by 26 per cent from 4.2 l to 3.1 l.

On either side, the tidal air presented a larger part of the vital capacity in the presence of a pneumothorax than before induction of the pneumothorax, indicating a diminished ventilatory reserve.

In analyzing these average values it must be stressed that a considerable scattering of figures exists, as one might well expect in a group of patients who were not homogeneous as to duration and extent of pneumothorax, amount of involvement in the collapsed and in the contralateral lung and as to the presence of adhesions, mobility of mediastinum, etc. However, the average values quoted are indicative of the general trends.

The important deductions to be made are as follows:

(1) Collapse (by pneumothorax) reduces the oxygen intake of the collapsed lung; this reduction is caused partly by a decreased minute volume and partly by a less efficient use of the ventilated air, as indicated by an increase in ventilation equivalent.

(2) The reduction in oxygen intake is compensated for by an increased intake of oxygen through the contralateral lung.

(3) This increase is achieved by some increase in the minute volume; but the increase in minute volume (a measure of ventilatory work) is considerably smaller than the increase in oxygen intake (the average being 16 per cent as against 30 per cent). A better utilization of the ventilated air, as indicated by a drop of the ventilation equivalent, is a second factor in compensation.

(4) In a large proportion of cases of unilateral pneumothorax, the contralateral effect of collapse is manifested by the reduction in the vital capacity and its subdivisions of the contralateral lung.

The reduction of function in the collapsed lung is compensated for not simply by a commensurate increase of the ventilatory work of the contralateral lung but, to an important degree, the compensation is achieved through a cardiovascular factor. This observation provides a sound physiological basis for the clinical experience that "the burden on the contralateral lung" is not as serious as it was assumed to be in the early phase of pneumothorax work.

According to animal experiments and clinical observations, in the presence of a normal contralateral lung, a normal cardiovascular system and a fixed mediastinum, ventilation remains competent at least under basal conditions, following the removal of one lung. From this it follows that, if a patient with unilateral pneumothorax is dyspneic at rest, the cause is not likely to be found solely in the degree of pneumothorax collapse. It has to be looked for in the contralateral lung (pleural obliteration, emphysema or other pathological pulmonary conditions) or in the cardiovascular system, provided a mobile mediastinum, causing too much contralateral collapse, can be excluded. Ipsolateral or contralateral bronchial stenosis must be ruled out as well.

A large number of lungs which were "reëxpanded" following pneumothorax treatment were studied. Many of these showed severely impaired function. There are essentially two causes for this condition: (1) incomplete reëxpansion of the lung with contraction of the hemithorax, shift of the mediastinal structures to the pneumothorax side and emphysema of the contralateral lung (i.e., different degrees of fibrothorax); and (2) pleural obliteration with the adverse functional effects, mentioned before. The first condition is clinically and roentgenologically obvious; the second is not and is, therefore, deceiving.

Thoracoplasty. We have studied 26 patients by bronchospirometry before and several months following the completed operation. The total pulmonary function, as determined by spirometry, was as follows: With very

few exceptions the oxygen intake did not show any significant change. The minute volume, again with few exceptions, did not change materially. The vital capacity and its subdivisions were markedly decreased in practically all cases. The ventilatory reserve, as indicated by the maximum breathing capacity, was decreased by more than 10 per cent in half the patients.

The average decrease of oxygen intake in the collapsed lung of 18 thoracoplasty patients was 20 c.c. The maximum decrease of oxygen intake was 100 c.c., but in seven of these 18 patients the decrease was less than 10 c.c. (in two there was an actual increase).

Since the average decrease of oxygen intake in the lungs collapsed by thoracoplasty is quite small, the compensatory mechanism is less obvious than in pneumothorax. However, the study of individual cases indicates that the principal mechanisms are the same as in pneumothorax.

In comparing the two collapse procedures, it is probably significant that in lungs collapsed by pneumothorax, the average of the ventilation equivalent rose from 2.9 l to 3.7 l whereas in lungs collapsed by thoracoplasty, it did not show any significant change (4.1 l before, 4.0 l after). In the latter group of patients, the ventilation equivalent decreased very markedly in a few patients (i.e., from 10.3 l to 1.9 l; from 5.4 l to 3.1 l), indicating that thoracoplasty may bring about a particularly successful selective collapse of functionally severely impaired portions. Much larger series of patients must be studied in order to decide whether the apparent functional superiority of thoracoplasty over pneumothorax is real or simulated by random sampling.

Influence of Different Postures on Pulmonary Function

Jacobaeus did repeated bronchospirometric studies on normals when they were lying on their back and on either side. He found that the ventilation and the oxygen consumption were higher on the side on which the subject was lying. Gebauer saw no change of the function of the right side and a slight decrease of the tidal air of the left side when a patient was turned on his left side. Vaccarezza, Lanari, Bence and Labourt [19] claim that the lung on the side on which the patient is lying has a higher oxygen intake, minute volume, vital capacity and complementary air than the other lung. Only the reserve air increased in the latter.

In table 2 vital capacities for each lung in six patients are given, measured in different postures of these patients. The distribution of the vital capacity between both lungs did not change consistently nor significantly when the patients changed their position from lying on the back to lying on either side. We do not have enough studies of the other respiratory data to be able to say whether or not they are influenced by change of posture. It is usually not possible to leave the bronchospirometry tube in place long enough to get good records in each position.

TABLE II

Bronchospirometric Determinations of Vital Capacity in Different Positions

Patient Number	Position	Vital Capacity c.c.	
		Right	Left
54	Lying on back	830	1040
	Lying on right	870	1120
	Lying on left	750	1160
55	Lying on back	1490	890
	Lying on right	1430	890
	Lying on left	1570	770
56	Lying on back	1680	430
	Lying on right	1820	410
	Lying on left	1780	460
62	Lying on back	1180	290
	Lying on right	1180	290
	Lying on left	1240	330
284	Lying on back	1510	1410
	Lying on right	1390	1280
	Lying on left	1450	1490
105	Lying on back	810	1530
	Lying on right	770	1470

INFLUENCE OF WEIGHT AND STRAPPING ON PULMONARY FUNCTION

It is commonly believed that the motion of one lung can be reduced when heavy weights are placed upon the respective side of the chest or when one hemithorax is strapped by several layers of adhesive tape. It seemed to be of interest to see what functional changes occur in lungs under such conditions.

In patients in whom the routine bronchospirometric studies had been done sandbags weighing six to 20 pounds were put on one side of the chest. The results of such studies on seven patients are presented in table 3. Moderate changes in oxygen consumption should not be taken into account, since records of only brief duration could be taken, a fact which makes an exact calculation of the oxygen consumption impossible. However, it is obvious that the oxygen consumption practically never decreases in the weighted side. Minute volume and tidal air increase more often than not. The vital capacity remains unchanged. Without any doubt, putting a weight on one side of the chest does not achieve a shifting of the ventilatory nor of the respiratory work from one lung to the other. If the excursions of the chest wall are diminished by the weight, the diaphragm increases its excursions. Ventilation (minute volume, tidal air) increases on either side, owing to the increased work the chest has to do in order to lift the weight.

In a recent paper, Leach [13] reports that he saw decrease of oxygen absorption in lungs which were compressed by sandbags. The observation

TABLE III

Effect of Sandbags on Ventilatory and Respiratory Function on Single Lungs

Patient Number	Weight of Sandbag and Side	Right Lung					Respirations per min.	Left Lung				
		O_2 intake per min. c.c.	Minute Volume c.c.	Tidal Air c.c.	Ventilation Equivalent l	Vital Capacity c.c.		O_2 intake per min. c.c.	Minute Volume c.c.	Tidal Air c.c.	Ventilation Equivalent l	Vital Capacity c.c.
72		196	4630	165	2.0	1390	28	148	4580	163	2.7	1800
	18 lbs. on right	203	5920	212	2.5	1330	28	175	6460	231	3.2	
	18 lbs. on left	185	5120	197	2.4	1330	26	148	5920	228	3.4	1700
95		95	3270	252	3.0	1260	13	200	3840	296	1.7	2110
	10 lbs. on right	95	4020	211	3.7	1260	19	200	3840	202	1.7	2110
	10 lbs. on left	95	4020	251	3.7	1260	16	200	3840	240	1.7	1930
170		203	6040	224	2.6	1530	27	88	4120	152	4.1	540
	20 lbs. on right	210	5490	211	2.3	1620	26	86	3840	148	4.0	480
	20 lbs. on left	191	5490	211	2.5	1530	26	73	3840	148	4.6	500
174		218	4610	329	1.8	1700	14	124	4170	291	2.9	1590
	20 lbs. on right	150	4390	439	2.5	1640	10	103	4120	412	3.4	1530
	20 lbs. on left	150	4780	341	2.7	1620	14	150	4390	342	2.5	1590
	20 lbs. on abdomen	150	4120	374	2.3	1590	11	113	3840	349	2.9	1530
224		133	4280	285	2.8	700	15	162	6040	402	3.2	1280
	6 lbs. on right	143	4390	314	2.7		14	190	6540	471	3.0	
	8 lbs. on right	133	4390	274	2.9		16	171	7140	446	3.6	
	10 lbs. on right	143	4390	274	2.9	700	16	162	7140	446	3.8	1280
	18 lbs. on right	152	4940	291	2.8		17	190	7720	454	3.5	
	6 lbs. on left	143	4390	259	2.7		17	162	7720	454	4.1	
	18 lbs. on left	133	5490	305	3.6	670	18	171	8780	488	4.5	1240
284		87	4580	268	4.5	1510	17	105	4670	274	3.8	1410
	16 lbs. on right	112	4660	389	3.5	1510	12	132	4390	366	2.9	1410
	16 lbs. on left	112	4660	359	3.5	1510	13	150	4390	338	2.5	1370
	16 lbs. on abdomen	112	4940	412	3.8	1450	12	132	4390	366	2.9	1430
409		328	6980	465	1.9	2630	15	61	3050	203	4.3	620
	15 lbs. on right	324	8320	520	2.2	2490	16	57	3230	202	4.9	580

that sandbags on one hemithorax do not decrease ventilation on that side should not necessarily be interpreted as meaning that such procedures are therapeutically without value, since they may well help to enforce more complete rest of the patient as a whole.

In two experiments (174, 284) sandbags (weighing 20 pounds and 16 pounds respectively) were put on the abdomen. This had no effect on oxygen intake, minute volume and vital capacity of either lung.

In three patients one hemithorax was strapped firmly with adhesive tape after routine bronchospirometric records had been taken (table 4). In one

TABLE IV

Effect of Strapping of One Hemithorax on the Ventilatory and Respiratory Function of Each Lung

Patient Number	Side Strapped	Right Lung					Respirations per min.	Left Lung				
		O_2 intake per min. c.c.	Minute Volume c.c.	Tidal Air c.c.	Ventilation Equivalent l	Vital Capacity c.c.		O_2 intake per min. c.c.	Minute Volume c.c.	Tidal Air c.c.	Ventilation Equivalent l	Vital Capacity c.c.
315	none	112	4940	198	3.8	1370	25	146	5210	209	3.1	1860
	left	112	4120	173	3.1	1040	24	150	4940	206	2.8	1370
326	none	80	4190	174	4.5	1060	24	99	3970	165	3.4	1240
	right	99	3430	137	3.0	990	25	136	4350	174	2.7	1180
109	none	219	4890	408	1.9	1720	12	94	4350	362	4.0	890
	right	225	5440	362	2.1	1800	15	103	4890	326	4.1	950

case (315) the vital capacity decreased on both sides practically by the same percentual amount (right, 24 per cent; left, the strapped side, 27 per cent). Only in one case (326) did minute volume and tidal air decrease somewhat on the strapped side and increase on the free side. From these findings we can conclude that strapping of the chest does not diminish pulmonary motion.

SUMMARY

By bronchospirometry functions and volumina of each lung are determined separately and simultaneously. The use of a soft rubber tube, instead of the metal bronchoscope, has made the method less uncomfortable for the patient and the results more reliable. Bronchospirometry is indicated whenever an irreversible operation on one lung is contemplated in order to determine the functional capacity of the contralateral lung. It also permits the study of various physiopathological problems.

No serious complication was seen in about 270 bronchospirometric examinations. The significance of the data obtained by bronchospirometry is discussed.

Spirometry may give nearly normal findings in patients in whom bronchospirometry reveals extensive damage of one lung and compensatory changes

in the other lung. Roentgen-ray and clinical findings do not permit definite conclusions as to pulmonary function.

Pleural involvement often causes severe functional damage of the lung, whereas parenchymal lesions may have relatively little effect on pulmonary function.

During pneumothorax treatment, the collapsed lung shows the following changes: decrease of oxygen intake, minute volume, tidal air, vital capacity, reserve air and complementary air; increase of ventilation equivalent.

Compensation is achieved by an increase of the oxygen intake in the contralateral lung. This is done only in part by increased ventilation; oxygen intake is further increased by a better utilization of the ventilated oxygen, i.e., a decrease of the ventilation equivalent.

The contralateral effect of unilateral pneumothorax is manifested by a decrease of the vital capacity, reserve and complementary air of the contralateral lung.

Thoracoplasty causes similar functional changes as does pneumothorax but, on the average, these changes are less severe following thoracoplasty than those during collapse by pneumothorax and, at least in some cases, less severe than those in lungs following the abandonment of pneumothorax.

Lungs reëxpanded following pneumothorax treatment frequently show extensive functional impairment.

Change in the patient's posture from the recumbent to the left or right side does not affect the percentage distribution of the vital capacity between the left and right lung.

Attempts at "immobilizing" a hemithorax by sandbags weighing up to 20 pounds and by strapping with adhesive tape do not achieve a reduction of the ventilation or respiratory work of the underlying lung.

BIBLIOGRAPHY

1. Bezançon, F., Braun, P., Soulas, G., and Cachin, M.: La division des airs. Examen fonctionnel des poumons séparés, Bull. Acad. de méd., Paris, 1936, cxv, 12.
2. Björkman, S.: Bronchospirometrie. Eine klinische Methode, die Funktion das menschlichen Lunge getrennt und gleichzeitig zu untersuchen, Acta. med. Scandinav., 1934, Supplement 56.
3. Brighton, G. R., and Barach, A. L.: Bronchospirometry, Ann. Otol., Rhinol. and Laryngol., 1938, xlvii, 4.
4. Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. I. Discussion of a physiological classification and presentation of clinical tests, Am. Rev. Tuberc., 1941, xliv, 26.
5. Cournand, A., Richards, D. W., Jr., and Darling, R. C.: Graphic tracings of respiration in study of pulmonary disease, Am. Rev. Tuberc., 1939, xl, 487.
6. Frenckner, P., and Björkman, S.: Bronchospirometry and its clinical application, with a short account of bronchial catheterization, Proc. Roy. Soc. Med., 1936, xxx, 477.
7. Gebauer, P. W.: A catheter for bronchospirometry, Jr. Thoracic Surg., 1939, viii, 674.
8. Jacobaeus, H. C.: Ergebnisse der Bronchospirometrie, Schweiz. med. Wchnschr., 1936, lxvi, 865.
9. Jacobaeus, H. C.: Bronchospirometry, Jr. Thoracic Surg., 1938, vii, 235.

10. JACOBAEUS, H. C., and BRUCE, T.: A bronchospirometric study on the ability of the lungs to substitute for one another. I, Acta med. Scandinav., 1940, cv, 193.
11. JACOBAEUS, H. C., and BRUCE, T.: A bronchospirometric study on the ability of the lungs to substitute for one another. II, Acta med. Scandinav., 1940, cv, 210.
12. JACOBAEUS, H. C., FRENCKNER, P., and BJÖRKMAN, S.: Some attempts at determining the volume and function of each lung separately, Acta med. Scandinav., 1932, lxxix, 174.
13. LEACH, J. E.: Abnormal pulmonary physiology as a result of chronic irradiation pleuropulmonitis. A preliminary report, Am. Jr. Roentgenol., 1943, l, 772.
14. LEINER, G., PINNER, M., and ZAVOD, W. A.: Bronchospirography. II. Application to collapse therapy: Preliminary report, Jr. Thoracic Surg., 1940, x, 32.
15. PINNER, M., LEINER, G., and ZAVOD, W. A.: Bronchospirography. III. The functional capacity of normal lungs, severely damaged lungs, lungs with strictly parenchymal lesions, thoracoplasty lungs, and re-expanded pneumothorax lungs, Jr. Thoracic Surg., 1942, xi, 241.
16. PINNER, M., and MARGULIS, A. E.: Physical principles in pneumothorax, Am. Rev. Tuberc., 1942, xlv, 676.
17. STEELE, J. D.: The practical application of bronchospirometry, Am. Rev. Tuberc., 1943, xlvii, 608.
18. VACCAREZZA, R. F., LANARI, A., BENCE, A. E., and LABOURT, F.: Examen funcional de cada pulmón por separado en tisiología, An. Cáted. de pat. y clín. tuberc., 1941, iii, 5.
19. VACCAREZZA, R. F., LANARI, A., BENCE, A. E., and LABOURT, F.: Influencia del decúbito lateral sobre el reposo pulmonar, An. Cáted. de pat. y clín. tuberc., 1941, iii, 254.
20. WHITEHEAD, W. K., O'BRIEN, E. J., and TUTTLE, W. M.: Studies of individual lung function. I. An open-circuit procedure with air and low-oxygen mixtures as the inspired gases, Jr. Thoracic Surg., 1942, xi, 266.
21. WRIGHT, G. W., and WOODRUFF, W.: Bronchospirography. Ventilation and oxygen absorption of normal and diseased lungs during nitrogen respiration in the opposite lung, Jr. Thoracic Surg., 1942, xi, 278.
22. ZAVOD, W. A.: Bronchospirography. I. Description of the catheter and the technique of intubation, Jr. Thoracic Surg., 1940, x, 27.

CASE REPORTS

DUODENAL ULCER WITH PERFORATION FOLLOWING A CUTANEOUS BURN; REPORT OF A CASE *

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Historical. "Dupuytren, in 1832, 10 years before Curling's article appeared, called attention to the change in the 'intestinal canal' which followed burns. Violent congestion, severe gastroenteritis, and 'more or less deep ulceration' were the conditions he found, depending on the length of time the patient had survived the accident. Long, in 1840, described two instances of fatal burns in which perforation of duodenal ulcers occurred." †

The term "Curling's ulcer," as Keeley [1] points out, has been adopted largely because his was the largest collection of cases yet published, and because his original paper described lesions occurring specifically in the duodenum, the site of the great majority of reported cases.

Incidence. Statistics vary greatly as to the incidence of duodenal ulcers following burns. There are many instances in which men with wide necropsy experience have never seen a case. In a report of 104 cases of cutaneous burns, Bancroft and Rogers [2] found that 28 per cent of the entire series were fatal, yet no instance of gastrointestinal ulceration was noted. Thirty-four per cent of their cases were under 10 years of age. Harris,[3] in a series of 138 fatalities, reported one death due to ulceration. Levin [4] found this lesion once in 13 years of autopsies. There is no record of a single case of gastrointestinal ulceration in a series of 171 cases of burns and scalds seen at Peter Bent Brigham Hospital in a 24 year period ending in 1937. Following the recent Cocoanut Grove disaster, 39 patients were sent to Massachusetts General Hospital. Autopsies were performed on six of these, three being dead on arrival, and three surviving from 40 to 62 hours. The gastrointestinal pathologic change was that of congestion and petechial hemorrhages in the fundic portion of the stomach and in the duodenum, though no ulceration was reported.[5] In Harkins' [6] exhaustive review of the literature in 1938, the first in 45 years, he included the following table. He concludes that the average of 3.8 per cent is probably near the correct figure for the incidence of ulcers following burns, but points out that there are many factors involved which make the statistics difficult to interpret.

These ulcers are commonest in children, the average age in Curling's series being 10.8 years. In Harkins' [6] collection of 94 necropsied cases since 1823, the average in 74 cases was 14.6 years, though cases have been reported in individuals 70 years of age. The age of the patient in our case was 68 years. In 65 of Harkins' [6] cases, 72 per cent were females.

The ulceration may occur at any time following the burn, though Maes [7] asserts that they are usually considered a late complication. McLaughlin [8] states

* Received for publication July 7, 1944.
† Quoted from KEELEY.[1]

TABLE I

Percentage of Duodenal and Gastric Ulceration Following Burns in Necropsied Cases

Author	Date	Number of Deaths Due to Burns	Number of Ulcers	Percentage Incidence of Ulcer
Long	1840	22	2	8.2
Curling	1842	11	4	36.4
Hewett	1848	17	3	17.7
Erichsen	1895	94	2	2.1
Simmonds	1898	50	2	4.0
Gruber (Strassburg)	1913	22	3	13.6
Gruber (Munich)	1913	19	9	0.0
Stewart	1923	115	2	1.7
Ronchese	1924	34	1	2.3
Harris	1929	138	1	0.7
Riehl	1930	152	5	3.3
Harkins	1937	4	1	25.0
		680	26	3.8

they usually appear in from two to 17 days following the burn, the average time being six to 12 days. Harkins [6] found that in 31 cases where the ulcer was associated with definite perforation or hemorrhage, death occurred in 12.8 days. Instances of ulceration occurring as early as 18 hours [4] and as late as 100 days [9] have been reported.

Etiology. The cause of "Curling's ulcer" is still awaiting experimental proof. The theories which have been advanced are limited only by the number of observers. Some of those which have received the most support are the following:

(1) "Curling suggested that Brunner's glands were called upon to perform the excretory functions for which the burned skin was incapacitated." (Quoted from Keeley.[1])

(2) The toxic theory, supported by Maes,[7] Robertson and Boyd,[10] and others, assumes that a toxin is carried to the intestines by the blood. Harris [3] feels that the pancreatic ferments digest and form ulcers in areas of necrosis formed by the burn toxins.

(3) McLaughlin's [8] experimental work of partially damaging the adrenals of 21 dogs produced ulceration in the small bowel of 17 of them, but no ulceration of the stomach was observed.

(4) The embolic theory with the infarcted area becoming necrotic and falling away is said to have been supported by Bilroth. Others, however, have called attention to the fact that emboli never occur in the duodenum without occurring also in the stomach, and point out also that the obstructed vessel has never been found.

(5) The subsequent development of duodenal ulcers following infection of the burned area has been noted by many. Stewart [11] states that "bacterial infection and intoxication is undoubtedly the most important direct cause of acute gastric and duodenal ulcer." He feels that ulcers following burns are less frequent than formerly because of asepsis. The extensive report of Perry and Shaw [12] includes 18 cases of duodenal ulcers collected from the Guy's Hospital records and three from other sources. The Guy's Hospital cases gave a ratio

of 18 septic ulcers to 52 from all causes and they came to the conclusion that duodenal ulceration is associated with septic conditions as frequently as it is with burns. They felt that the mechanism of production of the ulceration was the same in both cases.

(6) Recent experimental work by Necheles and Olson[13] may throw some light on the pathogenesis of this type of ulcer. In their experiments on dogs, they found that the volume of gastric secretion following burns was increased considerably if intravenous infusions of a saline-glucose solution were given, whereas there was no appreciable increase if no fluids were administered. Feeding before the burn resulted in an increase in the volume and the free acid of the gastric secretions. They suggest that these findings may have a relation to burns in human beings who at the time of the burn are generally in the absorptive phase of digestion and usually receive large amounts of fluids by mouth or by clysis. They found also a marked increase in the gastric motility which they conclude cannot be due to histamine for it is abolished by small amounts of atropine. They feel that this points to the presence of compounds of the nature of acetylcholine which may be liberated by the burn or that the acetylcholine-splitting esterase may be inhibited by the burn.

Pathology. In 1926, Pack[14] described the histopathology of these lesions conclusively. Duodenal ulcers following burns, he says, are generally single but may be multiple. The location varies; some pathologists believe generally in the upper transverse duodenum, and others find them in the descending part of the duodenum, close to the bile duct. The ulcers vary in size from a pinhead to a quarter. The amount of tissue lost may be great or slight as in some cases the lesion is but a mere erosion, whereas in others it is a rapidly sloughing, perforative process. The shape of the ulcer is irregular and dentate or long and narrow, occasionally circular. The edges are sharply and cleanly cut, the base is clean and grayish, and there may not be much inflammation at the margin. It is frequently funnel-shaped owing to a loss of more mucous membrane than muscle tissue. The outcome is perforation, hemorrhage, or spontaneous healing.

Case Report

The patient, a 68 year old white male, presented a history which went back to May, 1942, at which time he noticed some swelling of his legs. This became progressively worse and he entered the hospital November 14, 1942, with a chief complaint of swelling of his legs and belly. He had been troubled with dyspnea and orthopnea and had had some spells of palpitation. Regardless of treatment with digitalis, all the above symptoms had progressed. There had been no precordial pain but he had had occasional attacks of suffocating pain. There had been a weight loss of 30 pounds since May 1942, since which time his appetite had been poor. There had been occasional white colored stools. Further symptoms by systems were noncontributory.

He had had scarlet fever and otitis media. Pertinent family history was that his father died of cancer of the stomach and a sister died of diabetes.

Physical examination at the time of admission showed a fairly well developed white male of about stated age, with evidence of recent weight loss. He appeared anxious about his condition. Pertinent physical findings were fine, moist râles over the entire chest on auscultation. The apex of the heart was in the sixth interspace, 10 cm. to the left of the midsternal line outside the midclavicular line a mitral

systolic murmur was present. The abdomen was somewhat distended and a fluid wave was elicited. The liver edge was palpable 3 cm. below the right costal margin. The extremities were edematous. The pulse rate was 80; respirations 20; temperature 97.8° C.; and the blood pressure 140 mm. Hg systolic and 90 mm. diastolic. An impression was made of rheumatic heart disease with cardiac enlargement, mitral insufficiency, decompensation, and with a functional capacity of four.

The urine contained a few finely granular casts, but was otherwise negative. The hemoglobin was 91 per cent; the red blood cells, 4,570,000; and the white blood cells, 7,800. A chest film showed some congestion and marked enlargement of the heart to the left. An electrocardiogram taken on admission showed a rate of 82 per minute with an occasional premature contraction. The PR interval was prolonged. The QRS complex was at the upper limit of normal and was slurred. There was a left axis deviation and the ST segment was off the isoelectric line.

Treatment consisted of bed rest, proper digitalization, diuretics, and a salt free diet. He progressed very satisfactorily and was discharged December 2, 1942, with orders for one-half cat unit of digitalis per day. The electrocardiogram showed no appreciable change.

The patient was next seen on July 9, 1943, when he entered the hospital as an emergency following a gasoline burn on his left leg. Since his previous hospitalization, he had had but little dyspnea but had had some precordial pain on the right. There had been no orthopnea or ankle edema. There had been an additional weight loss of 10 pounds and some constipation. He had noticed a slight swelling in the right groin which was diagnosed by his family physician as a hernia and he had been wearing a truss. There were no additional complaints.

The patient appeared in much pain. There were first and second degree burns on the tip of the nose and both ears. The lungs were clear. The heart sounds were of good quality with regular rhythm. The apex was in the sixth interspace, 10 cm. from the midsternal line. Outside the midclavicular line there was a blowing systolic murmur heard best at the apex. There was no ascites or edema. There were second and third degree burns over the entire lower left leg extending down over the heel and covering most of the dorsum of the foot. The burn extended over the popliteal space up to one-third of the upper leg posteriorly. The blood pressure was 138 mm. Hg systolic and 80 mm. diastolic, temperature 98.6° C., respirations 34 per minute, and the pulse 116 per minute.

Blood studies on admission showed a red cell count of 4,970,000 and a white cell count of 17,400, with a hemoglobin of 103 per cent, values which were quite constant for his hospital stay. The urine was negative. An electrocardiogram was not taken.

Treatment consisted of immediate application of sulfadiazine ethanolamide to the burned areas, repeated at one-half hour intervals. In three days, a satisfactory eschar was formed. He was placed on a soft diet which he took well after the first few days. Aside from some urinary difficulties which he experienced for a few days, it was felt that his progress was very satisfactory, and he had no complaints except pain at times in the burned leg. Due to flexion, it was difficult to keep the eschar intact over the popliteal area and upper leg, so vaseline gauze dressings were applied to those areas on the tenth hospital day. The patient was allowed up in a wheel chair following the eleventh day and on the twentieth hospital day, he was allowed to take a tub bath to try to loosen the eschar. On the twenty-third day, wet dressings were applied to the leg and saturated regularly with physiological saline in a further attempt to loosen the eschar, small pieces of which were removed from the edges as they became less adherent.

At 2:00 p.m. on his twenty-third hospital day, he complained of nausea and there was emesis of undigested food. It was felt that this might be the first sign of too much digitalis and it was discontinued.

At 9:00 p.m. of the same day, the patient complained of a sudden, severe pain in the epigastrium which radiated to the right scapula and to his back in general. His skin was cold and beads of perspiration stood out on his forehead. The abdomen had a board-like rigidity, slightly more on the right than on the left. There was a marked pulsation over the precordium though the heart tones were of poor quality. The pulse was weak. The blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. The clinical picture appeared to be that of acute cholecystitis, a coronary attack, or a perforated viscus. A pearl of amyl nitrite brought no relief and ¼ gr. of morphine sulphate with 1/150 of atropine was administered by hypodermic.

On the twenty-fourth hospital day the blood pressure was 40 mm. Hg systolic and 20 mm. diastolic and the pulse could not be felt. The abdomen had lost the board-like rigidity but was still firm. The temperature was 95.8° C. The pain was most severe in the right upper quadrant. There was marked hyperresonance on the right extending up to the fifth rib and a flat plate of the abdomen disclosed a large gas bubble under the diaphragm. The blood pressure was low all day, the patient continuing to be in extreme shock. Later in the day, he complained of severe pain in the lower abdomen and physical examination revealed a markedly dilated stomach. During an attempt to insert a Levine tube, the patient went into complete collapse and died at 7:30 p.m. on the twenty-fourth hospital day.

Necropsy Report

Gross Examination. External Examination: The body was that of a 68 year old man weighing 100 pounds and 168 cm. in height. The subcutaneous fat was generally deficient over the limbs and thorax. The pupils were equal and measured 5 cm. in diameter. There were complete upper and lower dentures. The left leg was covered by a thick, tough, grayish eschar extending from below the knee to the level of the malleoli.

Internal Examination: Thorax: The pleural surfaces were smooth and glistening. The lung tissue was well aerated and normal grossly and on cut section.

Heart: The pericardial surfaces were smooth and glistening and the pericardial sac contained about 20 c.c. of clear yellow fluid. The heart weighed 490 grams. The right ventricle measured 7 mm. in thickness, the left, 15 mm. The mitral valve was slightly dilated but there was no gross evidence of any involvement of its leaflets or those of the tricuspids. The aortic valves were normal except for two small, calcified nodules, 1 by 2 mm. in size at the base of the right anterior cusps. The coronary vessels were patent and only slightly sclerotic.

Abdomen: The abdomen was slightly distended and on being opened, some gas escaped from the cavity. There were about 500 c.c. of a dark brown, thin, opaque fluid in the abdominal cavity. The intestinal surfaces were generally dulled and injected, the latter being most marked over areas of the small bowel lying in the false pelvis. There was an area of inflammation and fibrous adhesions lying between the anterior, superior aspect of the pylorus, the falciform ligament, and the underside of the anterior edge of the left lobe of the liver. Pressure on the stomach caused brownish, opaque fluid to appear in this region. Blunt dissection revealed a punched-out round hole, 5 mm. in diameter, on the anterior, superior aspect of the duodenum, just about at the junction of the pyloric sphincter and extending through all coats of the intestine (figure 1). This ulcer showed no inflammation and little evidence of fibrosis and scarring (figure 2). About one-half inch distal, there was another area of superficial ulceration with an inflammatory margin about 5 mm. in diameter (figure 2). The mucosa of the stomach along the lesser curvature showed multiple pin-point ulcerations and hemorrhages in the mucosa (figure 3).

Intestines: The serosa of the intestines showed patchy areas of inflammation throughout, especially so in those portions of the ileum lying low in the abdomen. There was not much gas or fecal material in the intestines. There was no evidence of mesenteric thrombosis.

Spleen: The spleen weighed 120 grams and was grossly congested. On cut surface, there was some evidence of fibrosis and the cortex bulged slightly beyond the capsule. The capsule was not thickened.

FIG. 1. Duodenal ulcer, serosal surface.

Kidney: The right weighed 110 grams; the left, 115 grams. There were several cysts ranging in size from 5 mm. to 1½ mm. in diameter in both kidneys. There was little evidence of any lobulation and the cortex was not thickened. There was good differentiation of the markings. There was some evidence of arteriosclerotic patches over which the capsule was adherent. The right kidney showed an area of about ¾ by 1 cm. where the cortex was thinned and had been replaced by fibrous tissue.

Liver: The liver was not removed. It was normal in size and the edge was sharp but somewhat softened. The cut surface showed gross evidence of congestion.

Anatomical Diagnosis: (1) Acute ulceration of the duodenum with perforation.

(2) Generalized peritonitis. (3) Cardiac enlargement. (4) Renal arteriosclerosis and polycystic kidney disease.

Microscopic Examination: Kidney: The interstitial tissue showed extensive fibrosis and infiltration of lymphocytes; the glomeruli and tubules showed atrophic changes. The interlobular arteries were thickened and the lumina of some were occluded. Some of the glomeruli were completely hyalinized.

FIG. 2. Duodenal ulcer; mucosal surface.

Liver: The liver was congested. The liver cells showed cloudy swelling and many contained a fine, greenish-yellow pigment. The capsule was thickened and infiltrated with lymphocytes except superficially where there were a few polynuclear neutrophiles.

Pancreas: The pancreas was somewhat atrophic and showed postmortem autolysis. The pancreatic duct contained bile pigment and the wall of the duct was infiltrated with inflammatory cell elements. The interstitial tissue was infiltrated with lymphocytes.

Intestines: The serosa was coated with fibrin and contained polynuclear neutrophiles.

Heart: The myocardium was infiltrated with a few polynuclear neutrophiles and lymphocytes. Some areas showed marked fibrosis and were infiltrated with lymphocytes and a few polynuclear neutrophiles. Some of the muscle fibers were hypertrophied and others were atrophied.

FIG. 3. Congestion and punctate hemorrhages of gastric mucosa.

Spleen: The spleen showed evidence of congestion.

Skin: The subcutaneous tissue showed necrosis with organizing thrombi in some of the larger vessels.

Lung: The alveolar walls were thin and the alveolar spaces were large.

Microscopic diagnosis: (1) Acute peritonitis. (2) Chronic myocarditis. (3) Subacute hepatitis. (4) Marked renal arteriosclerosis. (Microscopic examination by Dr. Pessin.)

SUMMARY

A general discussion of Curling's ulcer has been presented from the standpoint of the history, the incidence, the pathology, and some of the theories regarding the etiology of this lesion. Some of the recent experimental work has been included. A case of Curling's ulcer is presented which is of particular interest because of the fact that the burn was not of great extent; because there were no premonitory symptoms of the developing ulcer; and because of the diagnostic difficulties encountered due to previous cardiac and gall-bladder disease.

BIBLIOGRAPHY

1. KEELEY, J. L.: Gastrointestinal ulceration following burns, Am. Jr. Surg., 1939, xlv, 85.
2. BANCROFT, F. W., and ROGERS, C. S.: The treatment of cutaneous burns, Ann. Surg., 1926, lxxxiv, 1–18.
3. HARRIS, R. I.: Fatal burn: Death due to hemorrhage into the suprarenal capsule and to hemorrhage from a duodenal ulcer, Brit. Jr. Surg., 1929, xvi, 677–680.
4. LEVIN, J. J.: Duodenal ulcers following burns; with report of two cases, Brit. Jr. Surg., 1929, xvii, 110–113.
5. MALLORY, T. B., and BRICKLEY, W. J.: Pathology: with special reference to the pulmonary lesions. Symposium on the management of the Cocoanut Grove burns at the Massachusetts General Hospital, Ann. Surg., 1943, cxvii, 883.
6. HARKINS, H. N.: Acute ulcer of the duodenum (Curling's ulcer), as a complication of burns; relation to sepsis, Surgery, 1938, iii, 608.
7. MAES, U.: Curling's ulcer (duodenal ulcer following cutaneous burns), Ann. Surg., 1930, xxi, 527.
8. MCLAUGHLIN, C. W.: The Curling ulcer. Study of intestinal ulceration associated with suprarenal damage, Arch. Surg., 1933, xxvii, 490–505.
9. SIMPSON, J. C.: Brit. Med. Jr., 1923, ii, 1875–1889.
10. ROBERTSON, and BOYD: Toxemia of severe superficial burns, Jr. Lab. and Clin. Med., 1923, ix, 1–14.
11. STEWART, M. J.: Pathology of gastric ulcer; etiology of peptic ulcer, Brit. Med. Jr., 1923, ii, 955–957.
12. PERRY, E. C., and SHAW, L. E.: On diseases of the duodenum, Guy's Hosp. Rep., 1894, l, 171–308.
13. NECHELES, H., and OLSON, W. H.: Experimental investigation of gastrointestinal secretions and mobility following burns and their relation to ulcer, Surgery, 1942, xi, 751.
14. PACK, G. I.: Pathology of burns, Arch. Path. and Lab. Med., 1926, i, 767.

LONGEVITY WITH METASTATIC CARCINOMA OF THE STOMACH *

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THERE is considerable evidence that carcinoma of the stomach may manifest itself as a disease of marked chronicity.[1] Subsequent to metastases (especially to bones), however, the downward course is accepted to be relatively rapid. For this reason operative procedures for the alleviation of the primary lesion are undertaken with reluctance when metastases are demonstrable. A case is pre-

* Received for publication November 22, 1943.
From the Hematological Laboratory, Cook County Hospital, Chicago, Illinois. Aided by a grant from the Wilson Laboratories.

sented here with metastatic carcinoma demonstrated in the bone marrow three years before death, to reopen for question the validity of extreme surgical conservatism in the presence of metastases.

Case Report

A 62 year old white male entered the Cook County Hospital on September 15, 1939 because of weakness and dizziness (one week); vomiting of blood (one day); and a 20 pound weight loss (three–four months). He had been treated for peptic ulcer for 19 years, but during the last eight or nine years epigastric pain frequently associated with melena had been especially marked. His father and brother died of cancer. Noteworthy findings on examination were marked pallor, moderate emaciation, slight atrophy of the tongue papillae, a soft, inconstant apical systolic murmur, and moderate tenderness over the epigastrium and descending colon. The liver was palpable 3 to 4 cm. below the costal margin.

Blood findings on admission were: erythrocytes 1.34 million; hemoglobin 3.5 gm.; leukocytes 16,000; neutrophiles 66; lymphocytes 24; eosinophiles 2; monocytes 8. The red cells showed anisocytosis, poikilocytosis, hypochromia and polychromatophilia. Ewald meal: free acid 0°; combined acid 9°; lactic acid negative; blood ++. Stools (6): persistent occult blood (+ to ++++). Non-protein nitrogen: 71 mg.; Kahn reaction negative.

Proctoscopy (25 cm.): negative. Gastroscopy: pylorus and angulus normal, except for hypertrophic gastritis seen throughout stomach. Roentgen-rays: increased hilar markings with calcification of lymph nodes in chest. No abnormalities in esophagus, stomach, duodenum or colon. No evidence of metastases in skull, pelvis, or long bones.

Bone marrow aspiration biopsy (sternal): "The marrow is hyperplastic and is characterized by a great number of undifferentiated cells. These cells are approximately 15–20 micra in diameter and their nuclei occupy from 70 to 80 per cent of the cell volume. The cytoplasm is deep blue in color, dense, and granular. The nuclei are lightly stained and contain a loosely woven chromatin network in which from 1–3 nucleoli are seen. These cells are frequently found in groups. Plasma cells and histiocytes are increased in number. The erythroid and granulocytic elements, as well as the megakaryocytes appear normal. Mitotic figures are not infrequent. Opinion: Invasion of the bone marrow by malignant cells."

Treatment consisted of blood transfusions (1,000 c.c.) and iron in addition to a bland diet. Improvement was marked and on October 18, 1939 he was discharged from the hospital.

When seen in the Out-Patient Clinic on December 6, 1939, he felt well except for occasional "gas" and sour eructations. At this time his red cell count was 4.48 million and his hemoglobin 14.4 gm. He was again seen in March 1940, but thereafter disappeared from observation.

On August 29, 1942, he reëntered the hospital because of right-sided chest pain, weakness, vomiting, and tarry stools (six weeks); 40 pound weight loss (five months); epigastric pain, aggravated by meat and alcohol, and relieved by sodium bicarbonate and bland foods (two years). At this time he was pale and emaciated, had a red, smooth tongue. Breath sounds were decreased over the lower lobe of the right lung. The ribs (third to the seventh) were soft and very tender on the right side, and the seventh was freely movable. There was tenderness in the epigastrium.

Laboratory findings of interest at this time were the increased phosphatase (8.65 and 15.2 units), no Bence-Jones proteinuria, normal non-protein nitrogen, stools (3) negative for occult blood. The blood findings were erythrocytes 3.92 million, hemoglobin 11.4 gm., leukocytes 7,000, neutrophiles 75, lymphocytes 25.

The roentgenographic examination of the chest cavity was non-contributory and that of the stomach was unsatisfactory because of the patient's inability to coöperate. The findings in the osseous system were: "evidence of a fracture of the seventh right rib . . . numerous oval areas of decreased bone density throughout the skull . . . possibility of multiple myeloma should be considered. Metastatic malignancy, however, is not ruled out . . . questionable area of decreased density in the right ischium."

Bone marrow biopsy at this time showed "the bone marrow . . . moderately cellular. . . . There is an occasional group composed of varying numbers of large, approximately 20 mu. sized cells, having round to oval nuclei which occupy ⅓ to ¾ of the cell volume. These cells have a grayish-blue granular cytoplasm and multiple small vacuoles. The nuclear chromatin is rather finely dispersed, and occasionally very distinct nucleoli can be seen. The number of nucleoli vary from 1 to 3. Comment: The cells above described, occurring as they do in groups and being distinctly atypical and foreign to the marrow, suggest a bone marrow replacement by metastatic neoplasm. It is interesting to note that bone marrow obtained from the patient on October 6, 1939, showed almost identical findings. The cells at present differ from those of the previous smear in that they are more vacuolated and apparently have fewer mitotic figures than previously encountered. It is difficult to conceive that a metastatic malignancy should have persisted for three years."

The course was progressively downward and on September 26, 1942, the patient died.

On postmortem examination a malignant ulcer, 5 by 6 by 0.6 cm., with well defined but undermined margins was found near the esophago-cardiac junction. Several peripancreatic and periaortic metastatic nodes, measuring up to 3½ cm., were seen. The liver was studded with metastatic nodules. The osseous system was diffusely infiltrated by small to large metastases. Both the primary ulcer in the stomach and the secondary lesions throughout the body were found histologically to be adenocarcinoma.

Discussion

The patient originally presented himself with the history of a peptic ulcer of 19 years' duration which had manifested itself by pain and bleeding. It is impossible to ascertain from the history when the transition from the benign to the malignant ulcer had taken place. The 20 pound weight loss antedating his admission by three or four months is the first clinical clue that significant change had taken place. It is improbable, however, that this would have been sufficient time to establish metastases. The hematological findings on this admission were compatible with acute bleeding superimposed on chronic bleeding, without casting light on the nature of the underlying lesion. The absence of free acid and the presence of blood in the gastric contents, as well as the persistent occult blood in the stools, all bespoke a malignancy. It is significant that neither gastroscopic nor roentgenographic examination revealed the lesion even though its presence at this time was confirmed by the finding of metastases. It is also noteworthy that on a bland diet and replacement therapy (iron) the blood findings became normal within a relatively short period of time. Though details in the interval are unavailable, no radical change had apparently taken place during the two and a half year period between his first hospital admission and the reappearance of prominent symptoms, which, except those secondary to extensive bone destruction, were similar to the original. It is somewhat surprising that the blood should have remained at an adequate level in spite of episodes of bleeding and so marked a displacement of the bone marrow, and should have com-

pletely lacked the characteristics ordinarily associated with myelophthisic anemias.

A feature of this case, of considerable clinical interest, is the transition from a benign to a malignant ulcer, a transition originally revealing itself clinically by extensive bleeding. At this time the lesion was so small (or so placed) as to be undiscoverable by either roentgen-ray or gastroscopy, and yet had already metastasized to bones so extensively as to be cytologically demonstrable. Of much more importance was the benign course for a two and a half year period following the demonstration of bone marrow metastasis. This raises the question whether extreme surgical conservatism is justified in the presence of demonstrable metastases, when otherwise operative intervention might be indicated for the alleviation of symptoms. It would appear, at least from this singular case, that primary surgical procedures when otherwise indicated are justified even though early metastases are demonstrable.

Summary and Conclusion

A case is presented in which metastatic carcinoma was demonstrated in the bone marrow three years before death.

It is suggested that metastases occur earlier in carcinoma than has hitherto been believed.

The attitude towards surgical intervention in the presence of metastases may bear reëvaluation.

BIBLIOGRAPHY

1. Palmer, W. L.: The duration of gastric cancer, Gastroenterology, 1943, i, 723.

HEREDITARY HEMORRHAGIC TELANGIECTASIA: REPORT OF TWO CASES*

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Hereditary hemorrhagic telangiectasia is a rare disease, first recognized by Osler,[10] and is characterized by the triad of multiple telangiectases; hemorrhage, or anemia; and a history of familial occurrence. Some 500 cases occurring in over 100 families have been described.[6]

The characteristic lesions consist of pin-point to pea-sized telangiectases occurring most commonly in the skin and mucous membranes, but have also been described in almost every organ-system in the body—gastrointestinal tract, genitourinary system, respiratory system, and brain. These telangiectases represent dilatation of the blood vessel walls which consist of a single layer of endothelium covered with a much thinned layer of epithelium. The lesions commonly make their first appearance about the end of the first decade of life in the mucous membranes and during the third and fourth decades in the skin.

*Received for publication December 6, 1943.

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The extreme fragility of the lesions and the time of their appearance largely determine the symptomatology of the disease. As the nasal mucous membrane is usually involved first, epistaxis occurs with increasing frequency from late childhood onward. In middle life the skin and visceral lesions appear and add to the blood loss. The resulting secondary anemia may be very severe, but the hemoglobin is seldom below 50 per cent. The skin lesions occasionally disappear after a period of years, but the anemia persists. As the patient ages, the quantity of blood lost increases and a hemorrhage from the nose of 1000–1500 c.c. is not uncommon. The 6 per cent mortality of the disease is associated with these hemorrhages.

The hereditary factor in the disease seems to be transmitted as a simple dominant by both sexes and may affect both sexes. Teahan [13] has traced the disease through six generations of one family. Fitzhugh,[3] however, has stressed the occurrence of atavism in this disease, citing seven instances in the 212 cases reported until 1923. In one of these, two and possibly more generations were skipped. As will be indicated later, Case 1 may represent an instance of atavism.

Case Reports

Case 1. F. L., 51 year old white male farmer, was first admitted to the medical service of the Indiana University Medical Center on March 31, 1941 with the complaints of weakness, loss of weight, abdominal pain after eating and shortness of breath.

The weakness had begun about six years previously and had progressed to the point where he was unable to work, or could scarcely carry on any of his usual activities. During this same period he had lost 25 pounds in weight.

Pain in the abdomen had begun three years before, occurring usually after meals, and was relieved by belching or soda. No hematemesis, melena, jaundice, or acholic stools had been noted. Progressively increasing dyspnea accompanied by palpitation had developed during the year previous to admission.

In the past the patient had suffered from the usual childhood diseases without complications, had influenza during the epidemic of 1918, and had typhoid fever and smallpox at the age of 21.

The family history showed his mother had died from cancer of the stomach and his father of a hemorrhage from the stomach or lungs. Two sisters and two brothers were alive and well.

The review by systems showed no difficulties aside from those listed in the present illness except some urinary frequency and nocturia four to five times. No associated hematuria, pyuria, or dysuria was present.

Physical examination revealed a pale, somewhat asthenic, middle-aged male, appearing chronically ill. The skin contained numerous telangiectases varying in size from 1 to 5 mm. These lesions were most abundant over the upper half of the face and ears, and the finger tips; but were also present in lesser numbers over the back, arms, legs, left great toe, prepuce and glans penis. The examination of the eyes was negative except for the presence of a similar lesion on the palpebral conjunctiva of the right eye. Telangiectases were also noted in the mucous membranes of the nose, throat and tongue. The heart was of normal size; rate and rhythm were regular. A systolic murmur was present at the apex. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The abdomen was moderately tender in both lower quadrants. No palpable masses were present. The liver was down two fingers' breadth. The extremities were negative except for slight pitting edema about the ankles.

Laboratory investigation revealed a normal urinalysis. Hemoglobin was 5.8 gm.; red blood cells, 3,130,000; white blood cells 3,700 with a normal differential count. Platelets were 126,000 to 187,000. Average red cell diameter was 8.29 micra. Icterus index was 10. Stools were 1 + for occult blood on April 8, 1941 and April 17, 1941. The sternal bone marrow obtained by aspiration was hyperplastic with evidence of an increase in megaloblasts and was considered to resemble that seen in the pernicious anemia group.

Roentgen-ray examinations of the upper gastrointestinal tract by barium meal revealed spasticity of the duodenal bulb. No niche was present and there was displacement of the second portion of the duodenum upward and to the left. A barium enema showed a normal colon. A gall-bladder series was negative.

The patient was discharged on April 19, 1941, undiagnosed, and was instructed to return to the out-patient clinic in two months. The patient failed to return at the specified time and was not seen again until October 7, 1942. At that time he stated that for six months after leaving the hospital he felt fairly well and had been able to carry on his work but then had become progressively weaker, until at this time taking only a few steps completely exhausted him.

The remainder of his complaints were essentially the same as on his previous admission except that his urinary frequency was now accompanied by some dysuria.

Physical examination revealed little change except a loss of weight from 111 to 105 pounds.

Laboratory examination at this time showed a normal urinalysis. Hemoglobin was 6.5 gm.; red blood count 3,710,000, white blood count 6,650 with a normal differential count. Blood volume index was 0.84, color index 0.58 and saturation index 0.69. Platelets were 130,200. Bleeding time was 2½ minutes; clotting time 4½ minutes, with normal clot retraction. Icterus index was 5. Van den Bergh direct reaction was negative; indirect less than 0.1 mg. per cent bilirubin. Stools were 4 + for occult blood. Gastric analysis by the alcohol-histamine technic revealed adequate free HCl and was positive for blood in all fractions. Serologic reactions were negative. Phenolsulfonphthalein excretion was 30 per cent in 15 minutes and 21 per cent in 30 minutes. Sternal bone marrow showed a very mild hyperplasia.

This time the nature of the patient's condition was recognized and upon further questioning it was found that the patient had suffered from nose bleeds since the age of six years, although these had not become frequent until about the age of 12–14. The telangiectases on his face had first appeared at about the age of 40, and those on his fingers had followed a few years later. These lesions were known to bleed profusely on very slight trauma. No family history of similar lesions could be obtained among the patient's ancestors or among his own children. In spite of the fact that his father died of hemorrhage, the patient did not believe that he suffered from a similar condition.

Although it was felt that the blood in the stools could be explained by that observed in the posterior nasopharynx, a more thorough examination of the gastrointestinal and respiratory tracts was made. Telangiectases were seen in the mucous membranes of the nose and nasopharynx, uvula, mouth and tongue. Similar lesions were observed in the trachea, two in the right main stem bronchus, but none in the esophagus or portion of the stomach which could be observed with the esophagoscope. Proctoscopic examination revealed a small, reddened area approximately 5 mm. in diameter about 4 cm. in on the anterior wall which resembled the lesions seen in the skin.

A biopsy of one of the finger lesions showed very marked telangiectasia in the capillaries of the dermis.

The patient was placed on ferrous sulphate gr. 5 three times a day, and in nine days the maximum reticulocyte response of 3.4 per cent was reached. The hemo-

globin rose to 10 gm. and the red blood count to 4,980,000 on October 23, 1942. The patient was given one transfusion of 500 c.c. of blood on October 26, 1942, and on discharge the hemoglobin was 12.5 gm.

Case 2. A. S., 70 year old white laborer, has had six admissions to the Indiana University Medical Center because of severe epistaxis and associated anemia. When first seen on March 24, 1936 he was having small nose-bleeds every three to four days and severe nose-bleeds (500 c.c. or more) every five to six months. Since that time his severe epistaxis has become more frequent until he has now become a chronic invalid.

The patient's history dates back to 1874 when at the age of three he was butted by a ram and his nose broken. This was followed by severe epistaxis and throughout childhood epistaxis was frequent. During young adulthood he had little difficulty and was able to work as a manual laborer. In 1917, at the age of 45, he had influenza and following this he again began to have epistaxis. Also about this time he first remembers the presence of numerous telangiectases on his face which would bleed profusely if cut while shaving. In 1920 he was treated with radium at the Mayo Clinic, and between that time and 1936 he had radium four more times and cold cautery to the nasal septum numerous times. In 1934 he contracted syphilis and received four months' treatment of alternate arsenic and bismuth injections. Previous to his second admission to the hospital on December 18, 1938, he complained of hematuria and profuse hemorrhage from a ruptured telangiectasis on his face. In 1940 he had a small hemorrhage from his left eye.

Concerning his family history, he stated that his mother had telangiectases and that a daughter, age 43, had suffered from frequent epistaxes since childhood and had telangiectases on the face.

Physical examination on his last admission, September 4, 1942, showed a pale, undernourished, elderly white male. Telangiectases were present in the skin of the face, scalp, ears, chest, back, legs, glans penis, palms of the hands, sides of the fingers and toes, being most abundant over the face, ears, and fingers. Similar lesions were seen in the mucous membranes of the mouth, palpebral conjunctiva, and nose. The anterior half of the nasal septum was absent and three small arteries were once seen in the floor of the nose. Bilateral cataracts were present and the fundus could not be seen, but a note made by the resident in Ophthalmology in 1939 stated that there was an unusual pigment distribution with a piling up of pigment just superior to the left disk, resembling an old hemorrhage. Examination of the lung fields was negative. The heart size was within normal limits, rate 68, and rhythm regular. A rough systolic murmur was present at the apex but not transmitted. Blood pressure was 105 mm. Hg systolic and 60 mm. diastolic. The abdomen contained no masses or areas of tenderness. The liver and spleen were not palpable.

Direct laryngoscopy and bronchoscopy revealed a 3 mm. telangiectasis on the apex of the epiglottis, similar lesions on the left side of the trachea about the level of the fourth ring, and a minute spider lesion at the anterior extremity of the carina. The main stem bronchi and all bronchial orifices contained no lesions. Esophagoscopy was negative. Sigmoidoscopy revealed a vascular spider-like arrangement 12 cm. up in the left wall; 0.5 cm. above this network the channel was dilated to a size two to three times greater than that of the channels in the network.

During the seven years the patient has been followed, the hemoglobin has ranged from 3.2 to 10.5 gm., but has usually been between 5.5 and 7.5 gm. with red cell counts between 2.5 and 3 million. White blood cell and differential counts have been normal. Platelet counts were 320,000 to 370,000. Bleeding time was two minutes, clotting time five minutes and clot retraction complete in 90 minutes. Urinalyses have shown occasional red blood cells at infrequent intervals. Serologic reactions have been negative on each admission.

On his first and fifth admissions the nasal septum was cauterized with silver

nitrate, but in most instances his epistaxis has been so profuse that it has been impossible to locate the bleeding points. The patient has received 40 blood transfusions since being followed at the Medical Center, 10 of these being given during his last admission. During this admission from September 4, 1942 to January 25, 1943, he had 10 major episodes of epistaxis ranging in quantity from 100 to 850 c.c. His hemoglobin on this admission was 5.5 gm. Following nine transfusions it reached 10.5 gm. on December 3, 1942. The patient was unable to procure more donors and on discharge it had again fallen to 5.8 gm. Between episodes of severe epistaxis there was almost always a constant oozing of blood so that it could always be seen in the posterior nasopharynx.

Comment. As only one brother and the eldest son of the first patient could be examined, and the source of the father's hemorrhage cannot be determined, we are unable to decide whether this represents an instance of atavism. The two members of the family examined showed no telangiectases and the patient stated that none of his family suffered from frequent epistaxis or skin lesions similar to his. As the clinical picture of the disease is sufficiently clear, it may mean that this is another instance of atavism to be added to those already described, or it may be that as his children grow older, one or more of them may develop evidence of the disease.

Although lesions in the colon similar to those seen in these two cases have been described before,[4] the incidence of telangiectases in the remainder of the gastrointestinal tract is probably not as great as a cursory review of the literature would seem to indicate. Too many of these reports [7, 8] base their conclusions on the finding of occult blood in the stools. These conclusions hardly seem justified when it is remembered that varying amounts of blood may almost always be found in the nasopharynx of these patients and would certainly lead to a positive test for occult blood in the stools.

Only three observers have reported cases in which the presence of telangiectases in the stomach has actually been proved. Osler [10] in his original communication described one case at autopsy, but this man died of carcinoma of the stomach which might cast some doubt on the nature of the telangiectases. Boston [2] described two cases, in one of whom the lesions were seen at operation performed because of profuse gastric hemorrhage, and in the other the lesions were found at autopsy following repeated gastric hemorrhages. The sister of the second case also died of gastric hemorrhage. Both cases had the skin lesions and a positive family history. Renshaw [11] reported a case in which eight lesions were seen in the mucosa of the antrum, two on the angularis, and four on the lesser curvature of the stomach with the gastroscope. In the two cases reported here, no telangiectases were seen in the esophagus, or the portion of the stomach seen by the esophagoscope. Both cases did have symptoms somewhat suggestive of peptic ulcer, however, and in case 2 roentgen-ray examination was reported as suggestive of duodenal ulcer. Whether this lesion was associated with telangiectases remains to be proved.

Fitzhugh [4] described four cases of hereditary hemorrhagic telangiectasia, all of whom had hepatomegaly, splenomegaly, increasing intolerance to blood transfusions, and all were of blood type O. These conditions were not present in our cases, nor have they been noted in many other cases.[12] A possible explanation for this is advanced by Williams and Snell.[14] They described six cases of telangiectasia associated with liver disease, one of which was hereditary, and

advanced the theory that the hereditary type of disease is dominant and the hepatic recessive.

Although our second patient complained of gross hematuria on one occasion, during his numerous hospitalizations he showed only microscopic hematuria and this rarely. This apparently is characteristic of the disease as no cases with hematuria have been described in the American literature. Hereditary telangiectasia, however, possibly offers an explanation for some of the cases of so-called "essential hematuria." Blum [1] described a family in which the mother had severe nose bleeds, two of her children had hematuria, two had nose bleeds, and one was normal. Another of his patients, aged 53, had hematuria twice, then melena three times. No telangiectases were present on the skin, but he stated they had been present at about the age of 40 and then disappeared. Foggie [5] reported one case of hematuria in a patient in whom the skin lesions were present. There was a history of epistaxis on the mother's side of the family and the mother also probably suffered from hematuria. Keller [9] recorded the case of a child, age 9, who had one episode of hematuria, two of epistaxis, and another of hematuria within a year. Telangiectases were present on the nasal, oral, and pharyngeal mucous membranes, but none on the skin. There was a family history of epistaxis and hematuria extending back three generations. He noted that epistaxis and hematuria never occurred at the same time and expressed the belief that some families will show hematuria and other skin lesions, and that hematuria is the most common lesion in childhood and skin lesions the more common in the adult.

Although various forms of treatment have been advocated, none seems to be satisfactory. Cauterization of the bleeding points and radium packs have been advocated to control the epistaxis. The application of these treatments in Case 2 has resulted in necrosis of the septal cartilage and his bleeding continued, especially from small arteries coming up through the floor of the nose. It has also been suggested that if the anemia is adequately controlled the telangiectases will regress. This has not been our experience in these cases, and it has been impossible to maintain an adequate hemoglobin level except by very frequent transfusions. Treatment has, therefore, been symptomatic—using pressure packing to control hemorrhage, and ferrous sulphate for the anemia. The use of thromboplastic substances has seemed to reduce the frequency of hemorrhages, although there would seem to be no physiologic basis for this improvement.

Summary

1. Two cases of hereditary hemorrhagic telangiectasia have been presented.

2. Both cases have hemoglobin levels lower than those usually described in this disease; lesions in the skin, mucous membranes, upper respiratory tree, and colon. Case 2 had microscopic hematuria on rare occasions.

3. Case 1 may represent an additional instance of atavism in this disease but further proof is required before this conclusion can be reached.

4. Both cases have proved very refractory to the recommended forms of treatment.

Conclusions

In cases of recurrent epistaxis or chronic secondary anemia for which no cause can be ascertained, hereditary hemorrhagic telangiectasis should be con-

sidered and a search made for the characteristic lesions in the nasal, oral and pharyngeal mucous membranes. The presence of telangiectases in the skin and a family history of similar lesions or frequent epistaxis complete the diagnosis. Treatment of this condition at present seems to have little effect on the course of the disease.

BIBLIOGRAPHY

1. Blum, V.: Familiäre essentialle Hämaturia. Beitrag zur Frage der Oslerschen Krankhiet, Med. Klin., 1936, xxxii, 1254–1255.
2. Boston, L. P.: Gastric hemorrhage due to familial telangiectasis, Am. Jr. Med. Sci., 1930, clxxx, 798–802.
3. Fitzhugh, T.: The importance of atavism in the diagnosis of hereditary hemorrhagic telangiectasis, Am. Jr. Med. Sci., 1923, clxvi, 884–893.
4. Fitzhugh, T.: Splenomegaly and hepatic enlargement in hereditary hemorrhagic telangiectasis, Ibid., 1932, clxxxi, 261–268.
5. Foggie, W. E.: Hereditary hemorrhagic telangiectasis with recurring hematuria, Edinburgh Med. Jr., 1928, xxxv, 282–290.
6. Goldstein, H. I.: Hereditary multiple telangiectasis, Arch. Dermat. and Syph., 1932, xxvi, 282–308.
7. Goldstein, H. I.: Unusual gastrorrhagia or hematemesis: hereditary hemorrhagic telangiectatic Dysplasia with stomachorrhagia or gastrorrhagia, Am. Jr. Digest. Dis., 1938, v, 115–116.
8. Griggs, D. E., and Baker, M. Q.: Hereditary hemorrhagic telangiectasis with gastrointestinal bleeding, Am. Jr. Digest. Dis., 1941, viii, 344–347.
9. Keller, W.: Zur Kasuistik der Hämaturie in Kindesalter, Monatsschr. f. Kinderh., 1939, lxxix, 376–381.
10. Osler, W.: Family form of recurring epistaxis, associated with multiple telangiectases of skin and mucous membrane, Bull. Johns Hopkins Hosp., 1901, xii, 333–337.
11. Renshaw, J. F.: Multiple hemorrhagic telangiectasis with special reference to gastroscopic appearance (of stomach mucosa), Cleveland Clinic Quart., 1939, vii, 226–230.
12. Stellar, L. I.: Hereditary telangiectasis: Case, New England Jr. Med., 1942, ccxxvi, 336–338.
13. Teahan, W. W.: Hereditary telangiectasis occurring in 6 generations, Ann. Int. Med., 1939, xiii, 535–543.
14. Williams, D. H., and Snell, A. M.: Pulsating angioma (generalized telangiectasia) of skin associated with hepatic disease, Arch. Int. Med., 1938, lxii, 872–882.

TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS) MENINGITIS: CASE REPORT AND THERAPEUTIC EXPERIMENTS*

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Approximately 80 cases of *Torula histolytica* meningitis have been reported since 1861, when, according to Freeman,[1] Zenker recorded what was probably the first case. Less than half of the cases have been recognized before

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death.[2] It has been mistaken for tuberculous meningitis, brain abscess, brain tumor, encephalitis, lymphocytic choriomeningitis, and dementia paralytica. *Torula histolytica* is widely distributed in nature, having been isolated from wasp nests, stems of grasses and plants, bodies of insects, canned butter and milk.[3, 4] Lesions such as localized dorsolumbar abscess,[5] pelvic and inguinal abscess,[6] and nasopharyngeal ulcers [7] have been caused by *Torula histolytica*. Some [8, 9] are inclined to regard the injury to the body as resulting from mechanical pressure and a lytic secretion. Neither endotoxin nor exotoxin has been satisfactorily demonstrated. The body's defenses seem to be tissue immunity and local phagocytosis by cells of the reticuloendothelial system. In the humoral system only weak agglutinins have been demonstrated.[8, 10, 11] It is not known why the human body is not more frequently invaded by this widely disseminated yeast-like organism, but no doubt, as in bacterial infections, disease depends on the virulence of the invader as opposed to the resistance of the host. Rabinowitsch is reported by Rappaport and Kaplan [8] to have found only eight of 40 strains isolated from various sources in nature to be pathogenic.

Most cases occur in the third and fourth decades and twice as frequently in males as in females.[2] *Torula histolytica* meningitis has been considered to be invariably fatal, although recently Marshall and Teed,[12] in a preliminary report, present a case of apparent cure from sulfadiazine. However, not enough time has elapsed in this case to be sure, for the disease has been known to last as long as five years with spontaneous remissions only to end fatally. Gill [7] reported a case of orbital abscess with involvement of the ethmoid sinuses, the antrum and the hard palate. On one occasion Torulae were cultured from the blood. The patient recovered and is known to have been well for seven years.

The reporting of our case is felt to be justified since two therapeutic experiments were carried out, complete pathologic study made, the therapeutic effect of sulfadiazine on experimental infection in mice studied and the effect of sulfadiazine and penicillin on the organism in vitro observed.

Case Report

H. H., a 50 year old white man, was admitted to the Samaritan Hospital January 23, 1943 complaining of headache of five days' duration. It was located in the frontal region and radiated to both ears. The pain was stabbing, sharp and intermittent. It became progressively worse. He had not been feeling well for the previous eight months, tiring easily and suffering from nervous tension. A physician, whom he had consulted, told him he was having a "nervous breakdown" and advised complete rest. However, he continued work as a hairdresser until shortly before admission to the Hospital.

In 1939 a large portion of his stomach was resected for primary carcinoma and a cholecystectomy for biliary calculi was performed at the same time. A recent checkup at the Lahey Clinic, where the operation had been done, failed to show the presence of malignant disease. During World War I he spent two years in a Russian prison camp as a German prisoner, but had lived in the United States for the 20 years preceding admission.

Special inquiry and family history were noncontributory.

Physical examination showed the patient to be a middle-aged, apparently healthy man, lying comfortably in bed. Nutrition and development were good. The temperature on admission was 102.4° F. rectally, pulse 96, respirations 20 and blood pressure 110 mm. Hg systolic and 60 mm. Hg diastolic. The positive findings were:

(1) marked stiffness of the neck, (2) bilaterally positive Kernig sign, (3) inconstant Babinski and Chaddock reflexes in left foot, (4) slight blurring of the optic disk, (5) hyperactive reflexes.

Laboratory Data: On the day of admission the spinal fluid pressure was normal. The fluid contained 75 mg. of protein per 100 c.c. and had a reported cell count of 64 per cu. mm., of which 53 per cent were said to be lymphocytes and 47 per cent polymorphonuclears; but Torulae were mistaken for lymphocytes in this count. The blood contained 9,400 leukocytes per cu. mm. of which there were 85 per cent polymorphonuclears, 10 per cent lymphocytes, 2 per cent eosinophiles, 2 per cent basophiles and 1 per cent monocytes. Examination of the urine showed no abnormality. The complement fixation test for syphilis and the agglutination test for the presence of typhoid and paratyphoid antibodies made on the blood were negative. Roentgenograms of the chest showed only slight accentuation of the normal lung markings.

Several days after admission yeast-like organisms, at first thought to be contaminants, were cultivated from the spinal fluid. Two subsequent blood cultures and a second spinal fluid culture all yielded a heavy growth of the same organism, which was tentatively identified as *Torula histolytica* as it was non-sporulating, had no hyphae, was Gram-positive in young cultures and Gram-negative in older cultures. Later it was shown to be non-pathogenic to guinea pigs after two months and pathogenic to mice in 12 days. A sub-culture submitted to the National Institute of Health was identified by Dr. C. W. Emmons as *"Cryptococcus hominis."*

During the course of the illness the blood contained between 5,900 and 9,450 leukocytes per cu. mm. with no significant changes in the differential count. The blood contained 114 mg. of glucose per 100 c.c. when the patient was fasting. This determination was made with the thought that the Torulae might possibly act upon the glucose in the blood to cause hypoglycemia, although it was realized that under ordinary circumstances the organism does not ferment this sugar. Two days after admission the spinal fluid still showed no pressure changes. The fluid was reported to contain 38 cells per cu. mm., of which 63 per cent were polymorphonuclears and 37 per cent lymphocytes, but here again Torulae and lymphocytes were not differentiated. The spinal fluid contained 34 mg. of glucose and 75 mg. of protein per 100 c.c. The sedimentation of erythrocytes (Wintrobe method) was 10 mm. in one hour.

Treatment: Two blood transfusions, iodides orally and intravenously, and sulfadiazine (discontinued after four days as leukopenia threatened) caused no appreciable improvement. Gentian violet intravenously and thymol intramuscularly had been suggested for monilia infection of the lungs,[13] but to our knowledge had never been used in torulosis. Gomez-Vega [14] showed that gentian violet in 1/100,000 solution would inhibit the growth of Torulae in vitro. Accordingly 300 mg. of gentian violet in 5 per cent solution in distilled water were given intravenously daily for seven days. Since Myers [15] had found evidence of therapeutic activity of thymol in actinomycosis, we later used 180 mg. of this substance dissolved in 3 c.c. of olive oil intramuscularly daily for seven days. No benefit was noted following the use of either of these substances. Penicillin was unobtainable in sufficient quantity for adequate therapy.

Neal and Shapiro [11] found *Torula histolytica* meningitis refractory to the following treatments: autogenous vaccine, colloidal silver intrathecally, Fowler's solution orally, iodides orally and intrathecally and serum intrathecally, from rabbits which had received intravenous injections of Torulae. These authors found slight to no inhibition of growth in vitro in the presence of sodium iodide 1/500, sodium salicylate 1/500, colloidal silver 1/600, magnesium sulphate 1/500, rochelle salts 1/500, tricresol 1/1000 and quinine in saturated solution. A 1/10,000 solution of acriflavin caused well marked inhibition of growth and 1/5000 complete inhibition. Warvi and Rawson [16] suggested using acriflavin intrathecally in 1/10,000 solution. This was not done in our case since the infection was not confined to the meninges, but was

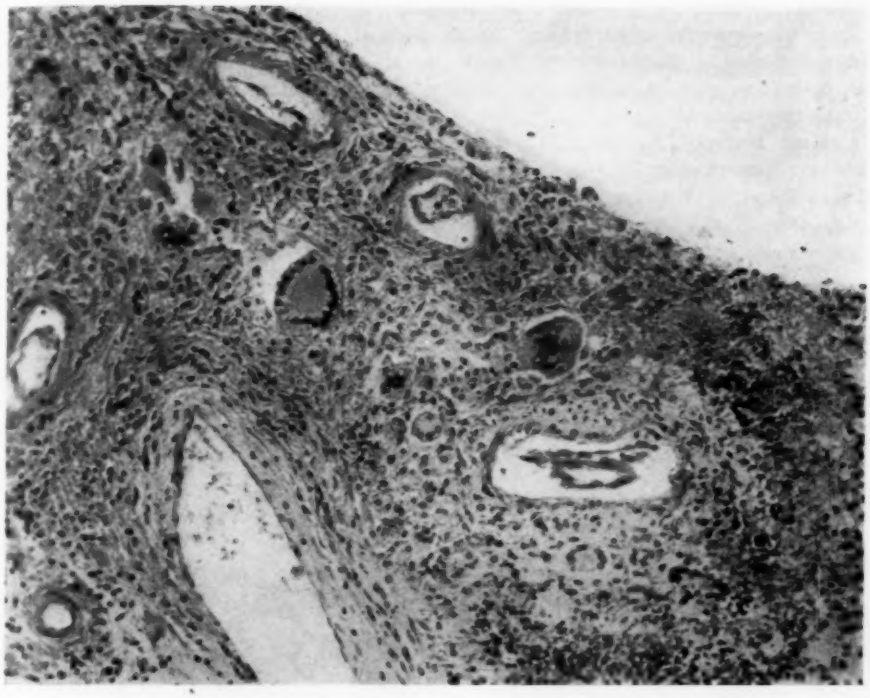

FIG. 1. Leptomeninges of upper cervical spinal cord showing inflammatory reaction. Lymphocytes, epithelioid cells, vacuolated giant cells and necrosis of exudate are seen.

generalized. Gentian violet was chosen rather than acriflavin because of its greater affinity for Gram-positive organisms.[17]

Course: Headache became more severe, hearing diminished, vision weakened and anorexia, loss of weight and weakness developed. At the end the patient was confused and bedridden and died in a convulsion 46 days after the onset of headache.

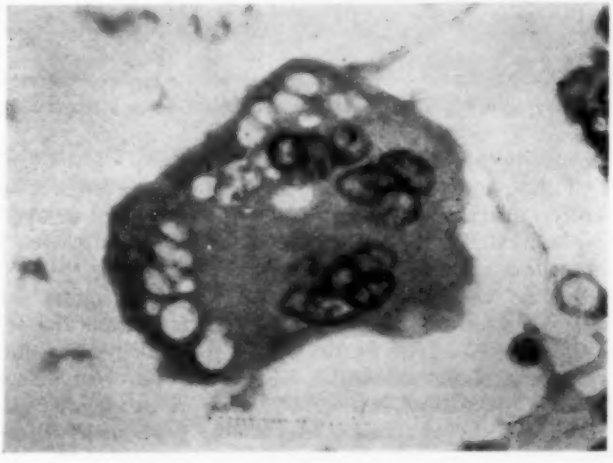

FIG. 2. Vacuolated giant cell containing Torulae in leptomeninges.

Autopsy. Autopsy was performed six hours after death. The brain, spinal cord and kidneys were the only organs which showed infection by Torula. Incidental findings included a diaphragmatic hernia on the left side and calcified mesenteric lymph nodes, as well as evidence of ancient, partial gastrectomy, gastrojejunostomy and cholecystectomy.

Central Nervous System: The dura mater was not tense and was of normal thickness. No increase in the amount of subdural fluid was noted. The leptomeninges covering the vertex, lateral, anterior and posterior aspects of the brain, were of normal thickness but there was a slightly increased amount of clear subarachnoid fluid. The blood vessels were slightly congested. The leptomeninges of

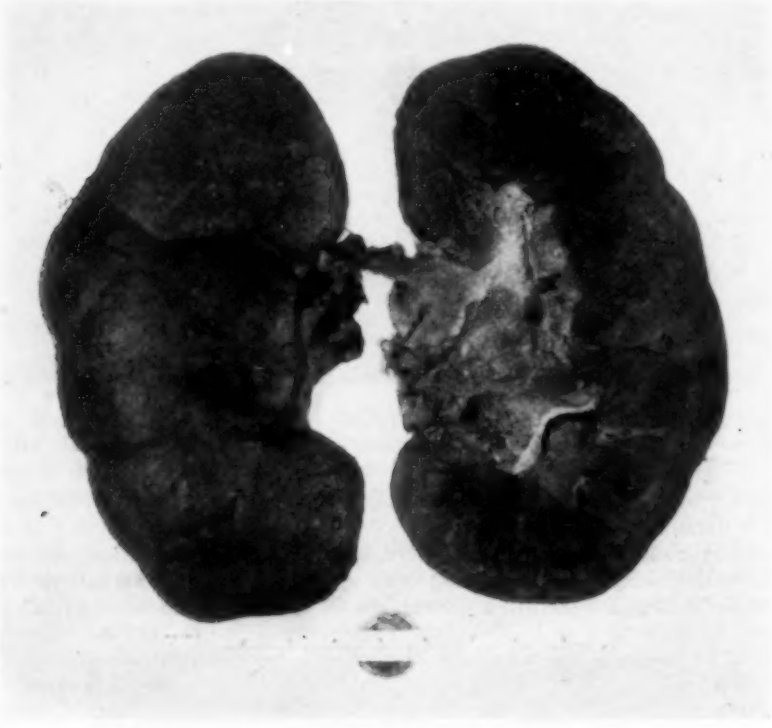

FIG. 3. Kidney showing multiple, miliary abscesses and intense congestion.

the under surface of the brain, particularly in the region of the optic chiasm, the anterior surface of the pons, the entire medulla and the under surface of the cerebellum, were slightly thickened and opaque due to the presence of a grayish exudate, which appeared to be located chiefly below the membranes. In places, however, some jelly-like, grayish-yellow material was found on the surface. The cranial nerves and the portion of spinal cord visible through the foramen magnum were surrounded by similar exudate. A pressure cone was not present. The brain, which was symmetrical, weighed 1510 gm. After hardening in formaldehyde solution further examination showed very slight dilatation of the lateral ventricles. The choroid plexuses were opaque and matted, while the lining of the ventricles was rough in places. A segment of the lower thoracic and lumbar portions of the spinal cord was negative on inspection. *Histologic examination* revealed the leptomeninges of basal portions of the brain and of all portions of the spinal cord to be greatly thickened as

a result of an inflammatory reaction characterized by the presence of large numbers of closely-placed, elongated cells with oval nuclei resembling epithelioid cells, lymphocytes and large numbers of giant cells (figure 1). In some places there was extensive necrosis of the inflammatory exudate. Large numbers of Torulae were found outside of and within giant cells (figure 2). The cranial nerves, the large nerves of the spinal cord and the meninges of the spinal cord supported similar inflammatory exudate. The reaction in the meninges was found to accompany branches of the meningeal vessels which entered the brain. The ependyma and choroid plexuses supported large amounts of exudate similar to that described in the meninges but in addition many polymorphonuclear leukocytes were present. In places the ependyma was very irregular in contour and sometimes broken. Beneath some of the breaks

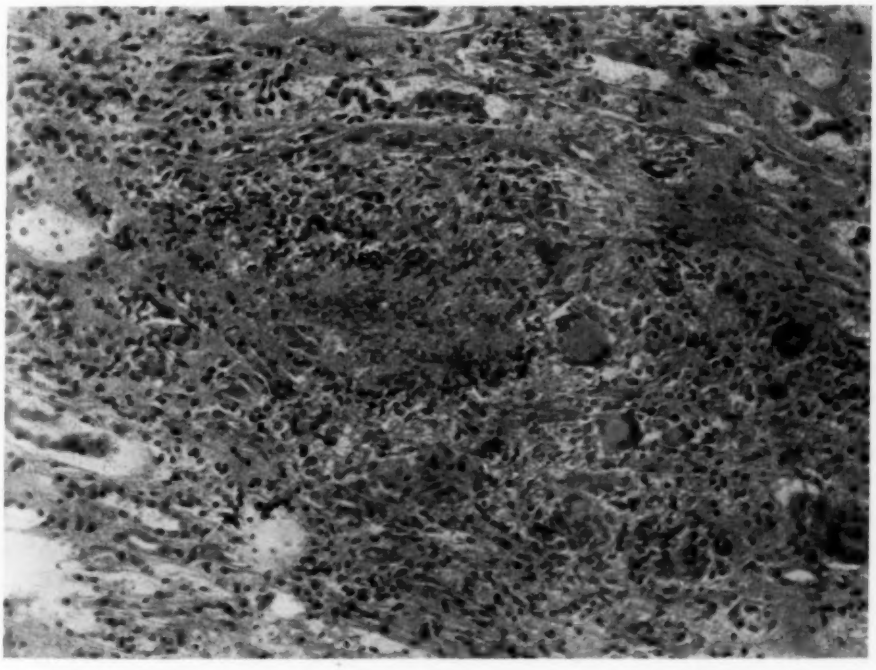

FIG. 4. Lesion in kidney resembling a miliary tubercle. Vacuolated giant cells containing Torulae are present.

there was proliferation of glial tissue, which extruded into the ventricle and accounted for the roughness described grossly. The brain substance and the substance of the spinal cord revealed nothing of note, except a few poorly-developed collars of lymphocytes around some of the vessels near the ependyma. Preparations of fluid from the lateral ventricles showed budding Torulae.

Kidneys: The right kidney weighed 230 gm., was very large, quite firm and dark purple. The capsule was easily removed and exposed a somewhat lobulated surface broken by the presence of numerous, slightly elevated, round, grayish lesions averaging 0.2 cm. in diameter. Similar lesions were found scattered throughout the cortex and medulla (figure 3). In places there were grayish streaks in the medullary portions. The pelvis was negative except for a few congested blood vessels. The left kidney weighed 250 gm. and was similar to its fellow. *Histologic examination* revealed numerous focal lesions characterized by the presence of giant cells and epi-

thelioid cells. The lesions were about the size of miliary tubercles and irregular in shape but tended to be elliptical. Some of the lesions simulated miliary tubercles in that they presented caseous centers surrounded by palisaded epithelioid cells. Peripheral to the palisaded cells were many unoriented epithelioid cells, some monocytes and large giant cells (figure 4). Some of the lesions contained large numbers of multinucleated giant cells but no evidence of necrosis. Torulae were found in large numbers within and outside of giant cells and occasionally within spaces lined by endothelium believed to be lymph vessels (figure 4).

Cultures at autopsy, taken from the vertex and base of the brain, the kidneys and blood, yielded *Torula histolytica*.

Experiments

Sodium sulfadiazine was added to a nutrient broth culture medium to give a concentration of 1 per cent, 0.1 per cent and 0.01 per cent. Three tubes of each concentration and three tubes of nutrient broth, each containing 1500 Florey units of penicillin, were inoculated with *Torula histolytica* and incubated aerobically at 36° C. Growth of the organism was abundant in each of the tubes at the end of four days. It would appear that neither sodium sulfadiazine nor penicillin inhibits the growth of *Torula histolytica* in vitro.

To determine whether or not sulfadiazine has any effect against Torulae in vivo, the following experiment was performed. Twenty mice were injected intraperitoneally with 1 c.c. of a 1 per cent suspension of *Torula histolytica* (approximately 100 million organisms) and left untreated. Another group of 20 were similarly injected, but, in addition, were given 0.4 c.c. of a 5 per cent solution of sodium sulfadiazine (20 mg.) subcutaneously daily. This dose was chosen after preliminary trials demonstrated that mice could tolerate this amount indefinitely. Bodansky [18] determined the m.l.d. for mice to be 1.5 gm. per kilogram of weight and Feinstone et al.[19] found the m.l.d. to be 1.2 gm. The dose we used was equivalent to 1 gm. per kilogram. The survival period of the untreated and treated groups is shown in table 1.

Table 1

Untreated

No. of Mice	Days Survived	Mouse-days
5	9	45
5	12	60
1	13	13
4	14	56
5	15	75
20		249

$$\text{Average} = \frac{249}{20} = 12.45 \text{ days}$$

Treated

No. of Mice	Days Survived	Mouse-days
8	3	24
2	4	8
5	5	25
3	6	18
2	7	14
20		89

$$\text{Average} = \frac{89}{20} = 4.45 \text{ days}$$

Because the dose of sodium sulfadiazine was so large, the experiments were repeated using smaller doses. Fifteen mice were injected as before with Torulae and left untreated. Another 15 were similarly injected and treated with 0.1 c.c. of a 2.5 per cent solution (2.5 mg.) of sodium sulfadiazine subcutaneously daily. A third group of 15 were likewise injected with Torulae but treated with 0.2 c.c. (5 mg.) of the sodium sulfadiazine solution subcutaneously daily. These amounts of sulfadiazine are equivalent to 0.1 to 0.2 gm. respectively per kilogram of body weight, a dose corresponding to that used clinically. The survival periods of these groups are shown in table 2.

TABLE II

Untreated

No. of Mice	Days Survived	Mouse-days
4	12	48
4	14	56
1	16	16
2	17	34
1	19	19
2	20	20
(1)*	—	—
14		193

$$\text{Average} = \frac{193}{14} = 13.8 \text{ days}$$

Treated with 0.1 c.c. of 2.5% solution of sodium sulfadiazine daily

No. of Mice	Days Survived	Mouse-days
1	8	8
1	9	9
1	10	10
2	12	24
3	13	39
3	14	42
1	15	15
1	17	17
1	23	23
(1)*	—	—
14		187

$$\text{Average} = \frac{187}{14} = 13.35 \text{ days}$$

Treated with 0.2 c.c. of 2.5% solution of sodium sulfadiazine daily

No. of Mice	Days Survived	Mouse-days
1	8	8
1	9	9
3	10	30
2	11	22
2	13	26
2	14	28
1	15	15
1	16	16
1	19	19
(1)*	—	—
14		173

$$\text{Average} = \frac{173}{14} = 12.35 \text{ days}$$

* One mouse in each group was still alive at the end of four weeks when the experiment was discontinued.

Discussion

From these experiments, in vivo and in vitro, it appears that sodium sulfadiazine has no demonstrable effect on Torulae. Penicillin does not appear to inhibit the growth of the organism in vitro. No known treatment is of proved value in torulosis. The organism is vigorous and resistant while the humoral defenses are apparently weak. Possibly one of the newly discovered antibiotics may be shown to be effective.

Summary

1. A case of *Torula histolytica* meningitis with postmortem findings has been presented.

2. Neither gentian violet nor thymol had any therapeutic value in this infection.

3. Experiments in vitro failed to demonstrate any growth-inhibiting effect of sodium sulfadiazine or penicillin on Torulae.

4. Experiments failed to show any therapeutic value of sodium sulfadiazine in experimental mouse infection.

The authors are indebted to Dr. Frances Hayward Smith for considerable assistance with the experiments and to Dr. O. W. Barlow of Winthrop Chemical Co., Inc. for supplying penicillin and thymol in oil.

ADDENDUM

Since this paper was submitted Dawson et al.* have included the *Cryptococcus hominis* in a list of organisms susceptible to penicillin. One of us (S. H. J.), now at the Lahey Clinic, with the assistance of Mr. H. J. Perkin, director of the clinic laboratory, confirmed the previous conclusion that our strain is not susceptible to penicillin. In tubes of nutrient broth containing respectively 10,000, 5,000, and 2,000 units of penicillin, growth was not grossly inhibited. Mice to which the organism proved fatal lived an average of 14.5 days, while mice treated with 80 units of penicillin approximately every three hours day and night for 12 days lived an average of 14.8 days, which is not significantly different.

Untreated

No. of Mice	Days Survived	Mouse-days
1	8	8
1	10	10
1	11	11
1	12	12
3	14	42
1	15	15
1	16	16
2	17	34
1	19	19
1	22	22
2 (living after 28 days)		
15		189

$$\text{Average} = \frac{189}{13} = 14.5 \text{ days}$$

* Dawson, M. H., Hobby, G. L., Meyer, K., and Chaffee, E.: Penicillin as a chemotherapeutic agent, Ann. Int. Med., 1943, xix, 707–717.

No. of Mice	Treated	Mouse-days
2	9	18
2	12	24
3	13	39
1	16	16
3	17	51
1	19	19
1	25	25
2 (living after 28 days)		
15		192

$$\text{Average} = \frac{192}{13} = 14.8 \text{ days}$$

BIBLIOGRAPHY

1. Freeman, W.: Torula infection of the central nervous system, Jr. f. Psychol. u. Neurol., 1931, xliii, 236.
2. Levin, E. A.: Torula infection of the central nervous system, Arch. Int. Med., 1937, lix, 667–684.
3. Jacobsen, H. P., Schamberg, J. F., and Morrow, H.: Fungous disease, 1932, Chas. C. Thomas, Baltimore, p. 253.
4. Klein, E.: Pathogenic microbes in milk, Jr. Hyg., 1901, i, 78–95.
5. Brewer, G. E., and Wood, F. C.: Blastomycosis of the spine; double lesion; two operations; recovery, Ann. Surg., 1908, xlviii, 889–896.
6. McGehee, J. L., and Michelson, I. D.: Torula infection in man, Surg., Gynec. and Obst., 1926, xlii, 803–808.
7. Gill, W. D.: Torula mycosis in man with special reference to involvement of the upper respiratory tract, with case reports, Trans. Am. Laryngol., Rhinol., and Otol. Soc., 1934, xl, 247–262.
8. Rappaport, B. Z., and Kaplan, B.: Generalized torula mycosis, Arch. Path., 1926, i, 720–741.
9. Stoddard, J. L., and Cutler, E. C.: Torula infection in man, Monograph No. 6, Rockefeller Inst. for Med. Research, 1916.
10. Hoff, C. L.: Immunity studies of Cryptococcus hominis (Torula histolytica) in mice, Jr. Lab. and Clin. Med., 1942, xxvii, 751–754.
11. Shapiro, L. L., and Neal, J. B.: Torula meningitis, Arch. Neurol. and Psychiat., 1925, xiii, 174–190.
12. Marshall, M., and Teed, R. W.: Torula histolytica meningo-encephalitis; recovery following bilateral mastoidectomy and sulfonamide therapy; preliminary report, Jr. Am. Med. Assoc., 1942, cxx, 527–529.
13. Queries and minor notes, Jr. Am. Med. Assoc., 1938, cx, 231.
14. Gomez-Vega, P.: Mycostatic studies on certain moniliae and related fungi, Arch. Dermat. and Syph., 1935, xxxii, 49–58.
15. Myers, H. B.: Thymol therapy in actinomycosis, Jr. Am. Med. Assoc., 1937, cviii, 1875.
16. Warvi, W. N., and Rawson, R. W.: Torula meningitis, Arch. Int. Med., 1942, lxix, 90–98.
17. Kolmer, J. A., and Tuft, L.: Clinical immunology, 1941, W. B. Saunders Co., Philadelphia, 1st ed., p. 284.
18. Bodansky, Oscar: Reduction of toxicity of 2-sulfanilamidopyrimidine (sulfadiazine) by phenylazo-alpha-alpha-diaminopyridine hydrochloride (pyridium) in the mouse, Proc. Soc. Exper. Biol. and Med., 1942, xlix, 216–218.
19. Feinstone, W. H., et al.: The toxicity, absorption, and chemotherapeutic activity of 2-sulfanilamidopyrimidine (sulfadiazine), Bull. Johns Hopkins Hosp., 1940, lxvii, 427–456.

EDITORIAL

THE ETIOLOGIC AGENT OF GRANULOMA INGUINALE

GRANULOMA inguinale (granuloma venereum) is a form of venereal infection which is common and widespread in the tropics, including the West Indies. Although rarely recognized in the northern United States, many cases have been observed in the southern states, particularly among the negroes. The lesions are usually limited to the genital regions and start as small vesicles or papules on the penis or labia minora, slowly spreading over the adjacent skin and mucous membranes. These lesions rupture or become excoriated, producing foul ulcerations covered with granulation tissue which may become exuberant and fungating. The lesions may be very mutilating, and they show little tendency to heal spontaneously, but except when modified by secondary infection they rarely involve the deep tissues, affect the lymph nodes, or impair the general health.

The most characteristic feature of the lesions microscopically is the presence of many mononuclear phagocytes containing inclusions which were first described by Donovan in 1905 and have since been known as Donovan bodies. These are small ovoid or short rod shaped bodies surrounded by a thick halo, or capsule, and are present often in large numbers in or around vacuolated areas in the phagocytes. They are Gram negative, but stain readily with Giemsa's or Wright's stain. Similar unencapsulated bodies are also found extracellularly in the lesions, and these may show bizarre variations in structure.

These bodies were regarded at first as protozoa, related to Leishmania. This view received some apparent confirmation from the fact that antimony compounds are therapeutically effective in this disease. Many attempts were made to cultivate organisms from the lesions, and in a number of cases cultures yielded bacteria related to the Friedländer bacillus, which have been designated *Klebsiella granulomatis*. Attempts to reproduce the disease with such cultures in animals and in human volunteers, however, were uniformly unsuccessful. More careful subsequent studies, notably by Johns and Gage [1] and by DeMonbreun and Goodpasture,[2] confirmed the constant presence and probable significance of the Donovan bodies, but no growth could be obtained on any ordinary culture medium, nor could lesions be produced in the usual laboratory animals or in the chorioallantoic membrane of the chick embryo. They used material aspirated from early unruptured lesions ("pseudobubos") which was rich in Donovan bodies but contained no other demonstrable organisms. Greenblatt, Dienst, et al.[3] confirmed these

[1] JOHNS, F. M., and GAGE, I. M.: Granuloma inguinale and cultural studies of Donovan bodies, Internat. Clin., 1924, iv, 15.

[2] DEMONBREUN, W. A., and GOODPASTURE, E. W.: Etiological studies of granuloma inguinale, South. Med. Jr., 1931, xxiv, 588.

[3] GREENBLATT, R. B., DIENST, R. B., PUND, E. R., and TORPIN, R.: Experimental and clinical granuloma inguinale, Jr. Am. Med. Assoc., 1939, cxiii, 1109.

observations, and with such material successfully reproduced the disease in four human volunteers.

More recently Anderson [4] and Anderson, DeMonbreun and Goodpasture [5] have reported the successful cultivation of the organism in the yolk of developing chick embryos from three human cases of granuloma inguinale. Inoculation of uncontaminated material into the yolk of developing embryos between the fourth and eighth day of incubation resulted in infection, the yolk removed four days after inoculation containing large numbers of morphologically typical encapsulated Donovan bodies. These were carried on indefinitely in serial cultures. When inoculated into older embryos, nonencapsulated forms with variable morphology were observed, like the extracellular forms in human lesions. The bodies also grew within the epithelial cells of the yolk sac, but did not invade any other tissues of the embryo.

Inoculation of laboratory animals, including rhesus monkeys, with such cultures produced no lesions. Attempts to produce the disease with these cultures in human volunteers have not been reported.

The organisms were cultivated in vitro in the fluid yolk aspirated from fertile eggs between the fourth and eighth day of incubation, viable embryo heart being necessary also for the first few transfers. They also grew in the water of condensation of agar slants containing 50 per cent of such yolk. They would not grow on coagulated yolk, or in the yolk of nonfertilized eggs. They evidently require some substances liberated by growing cells, although they are not obligate intracellular parasites. The nature of these substances is not known.

Anderson et al. regard the organism as a bacterium, bacillary in type, entirely unrelated to the Friedländer group, and differing from ordinary bacteria in its peculiar growth requirements. They have proposed for it the name *Donovania granulomatis*.

Anderson, Goodpasture and DeMonbreun [6] also studied the antigenic properties of the organisms. Heavy suspensions of organisms were obtained by centrifugalizing fluid yolk from infected eggs. The organisms were washed as free as possible from egg yolk and were killed by heating at 60° C. Intracutaneous injections of suitable dilutions of the suspended organisms caused typical hypersensitive reactions in six cases of granuloma inguinale, whereas no reactions occurred in four control cases. Less marked positive reactions were also obtained in these cases of granuloma inguinale with a filtrate of infected yolk, but not with filtrate of normal yolk.

Precipitin and complement fixation reactions were also carried out. These investigators noted that when the organisms were cultured serially in

[4] ANDERSON, K.: Cultivation from granuloma inguinale of microörganism having characteristics of Donovan bodies in yolk sac of chick embryos, Science, 1943, xcvii, 560.

[5] ANDERSON, K., DEMONBREUN, W. A., and GOODPASTURE, E. W.: An etiologic consideration of Donovania granulomatis cultivated from granuloma inguinale (three cases) in embryonic egg yolk, Jr. Exper. Med., 1945, lxxxi, 25.

[6] ANDERSON, K., GOODPASTURE, E. W., and DEMONBREUN, W. A.: Immunologic relationship of Donovania granulomatis to granuloma inguinale, Jr. Exper. Med., 1945, lxxxi, 41.

embryos inoculated on the fifth day of incubation, the yolk gradually acquired a ropy mucoid consistence, and the organisms showed capsules which were no longer compact, but appeared shredded and disintegrated, apparently disseminating into the surrounding medium. This mucoid material could be dissolved readily in dilute alkali and reprecipitated by dilute acid, and was thus separated and purified from most of the yolk. Dilutions of this material also gave positive intracutaneous reactions in four cases of granuloma inguinale, although quantitatively less marked than those obtained with suspensions of the organisms. Negative reactions were obtained in nine control cases.

Precipitin tests made by utilizing solutions of this capsular material and undiluted inactivated serum from 20 cases of granuloma inguinale were positive in 19 and negative in one. Similar tests with 66 control sera were negative in all but two, including five out of six cases with positive Frei skin reactions and 15 cases with positive serological reactions for syphilis.

Complement fixation reactions were positive in 12 of 15 cases of granuloma inguinale, and negative in 18 of 19 controls (excluding anticomplementary sera in both groups).

To check further the antigenic properties of the organisms, two hens were given repeated inoculations of infected yolk. Both gave positive intracutaneous reactions and positive precipitin reactions to the materials used in testing the human cases.

These tests, as pointed out by the authors, require further study and elaboration to establish their value as diagnostic procedures. They have shown a sufficiently high degree of specificity, however, to constitute strong evidence that the Donovan bodies are actually the causative agent of granuloma inguinale. The crucial test, reproduction of the disease in man by means of the cultures, remains to be carried out. Eventually attempts to do this will doubtless be forthcoming.

REVIEWS

The Reticulo-Endothelial System in Sulfonamide Activity. By FRANK THOMAS MAYER, Ph.D., Assistant Professor of Pharmacognosy and Pharmacology in the University of Illinois. 232 pages; 27.5 × 20.5 cm. 1944. The University of Illinois Press, Urbana, Illinois. Price, $2.50 paper bound; $3.00 cloth bound.

This doctor's thesis is a timely brochure on the sulfonamide drugs. The thesis gives an excellent review of the historical development of the sulfonamide drugs with more than 600 references. The various theories of the mechanism of action of the sulfonamides which have been held tenable from time to time are discussed and evaluated. Special reference is made to sulfonamide inhibitors such as para-amino-benzoic acid.

In the experimental portion of the thesis, the writer describes various technics employed to block the reticulo-endothelial systems of laboratory animals. For this purpose, he found the rabbit the most suitable animal. A colloidal solution of thorium dioxide (Thorodrast) served to provide a plethora of fine particles in the blood stream to blockade the reticulo-endothelial system. A carefully cultured strain of *Staphylococcus aureus* served as the infecting organism. In the rabbits, which had received intravenous injections of "Thorodrast" the administration of sulfathiazole produced urinary excretion of the unacetylated drug. In the normal animal, approximately 25 per cent of the compound was excreted in an acetylated form. It was concluded that the cells of the reticulo-endothelial system accomplish the acetylation.

Rabbitts unmedicated died within 24 hours after inoculation with the culture of the organism. These animals could be saved by sulfathiazole medication. In those animals inoculated with *Staphylococcus aureus,* whose reticulo-endothelial systems have been blockaded with "Thorodrast," sulfathiazole failed to save their lives. It was concluded that in any theory of sulfonamide activity, the reticulo-endothelial system of the host must be given a major consideration.

J. C. K., JR.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Chemistry and Physiology of Hormones. Publication of the American Association for the Advancement of Science. Publication Committee: HANS JENSEN, F. C. KOCH, and ABRAHAM WHITE. Edited by FOREST RAY MOULTON. 243 pages; 26.5 × 19 cm. 1944. American Association for the Advancement of Science, Washington, D. C. Price, $3.50 (to members); $4.00 (to others).

Proceedings of the Rudolph Virchow Medical Society in the City of New York. Volume III. 1944. Edited by the Publication Committee: FRANZ M. GROEDEL, M.D., BRUNO KISCH, M.D., and ERWIN SCHIFF, M.D. 103 pages; 25.5 × 18 cm. 1945. Brooklyn Medical Press, Inc., New York, N. Y. Price, $2.00.

Clinical Case-Taking. Third Edition. By GEORGE HERRMANN, M.D., Ph.D. 192 pages; 20 × 13 cm. 1945. C. V. Mosby Company, St. Louis. Price, $1.75.

The Doctor's Job. By CARL BINGER, M.D. 243 pages; 22 × 15 cm. 1945. W. W. Norton & Company, Inc., New York, N. Y. Price, $3.00.

Tropical Medicine. Fifth Edition. By SIR LEONARD ROGERS, K.C.S.I., C.I.E., LL.D., M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., and SIR JOHN W. D. MEGAW, K.C.I.E., B.A., M.B., Hon. D. Sc. (Queen's University, Belfast). 518 pages; 23.5 × 15.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, $6.50.

Radiologic Examination of the Small Intestine. By Ross GOLDEN, M.D. 239 pages; 26 × 18 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $6.00.

Clinical Roentgenology of the Digestive Tract. Second Edition. By MAURICE FELDMAN, M.D. 769 pages; 23.5 × 16 cm. 1945. The Williams and Wilkins Company, Baltimore. Price, $7.00.

The Specificity of Serological Reactions. Revised Edition. By KARL LANDSTEINER, M.D. With a Chapter on Molecular Structure and Intermolecular Forces by Linus Pauling. 310 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, $5.00.

COLLEGE NEWS NOTES

A. C. P. Board of Regents and Committees Will Meet June 9–10

The various committees, including the Committee on Credentials, of the American College of Physicians will meet at the Philadelphia Headquarters on June 9; the Board of Regents, on June 10. This meeting was postponed from the one first scheduled at St. Louis, May 3 to 5, owing to regulations of the Office of Defense Transportation. The regulations of the ODT still remain unchanged; hence, there is at present no prospect of an Annual Business Meeting for the election of Officers, Regents and Governors, nor of a meeting of the Board of Governors, because such a meeting would exceed in attendance the maximum of fifty, the limit set by the ODT. Present Officers, Regents and Governors will continue to serve until a regular election can take place.

All candidates whose proposals were executed and filed with the Executive Offices of the College by May 10, thirty days in advance of June 9, will be passed upon by the Committee on Credentials and the Board of Regents. Elections will be announced in these columns and formal notices will be mailed to each successful candidate as promptly as possible.

Oral examinations of the American Board of Internal Medicine for candidates from the eastern territory will be held at Philadelphia, June 6, 7 and 8. (See complete schedule later in the News Notes section of this issue.)

Additional A.C.P. Members in the Armed Forces

Dr. Elizabeth Brakeley, F.A.C.P., Montclair, N. J., has been commissioned a Major in the U. S. Public Health Service and will shortly go abroad in the service of the United Nations Relief and Rehabilitation Administration, to be gone for at least a year. This brings the total number of members who have entered upon military duty to 1,857.

The following members of the College have been honorably discharged:

Charles R. Castlen, Lieutenant Colonel, (MC), A.U.S.—Glendale, Calif.
Roger S. Mitchell, Jr., Major, (MC), A.U.S.—Glens Falls, N. Y.
W. Grady Mitchell, Lieutenant Commander, (MC), U.S.N.R.—San Angelo, Tex.

Lt. Comdr. J. LaMonte Zundell, (MC), U.S.N., Liberated from Bilibid Prison, Manila

Lt. Comdr. Zundell was among those rescued on February 4 from the Japanese Military Prison at Bilibid Hospital, Manila. Comdr. Zundell is an Associate of the College and was reported as a "prisoner of war" at the time of the fall of the Philippines. It was not until February 21 that his wife, in Grosse Pointe, Mich., learned of his rescue, as cables sent by Comdr. Zundell never came through. Finally notice came from the Bureau of Medicine and Surgery. She was totally unable to get direct communications to him, but early in March he arrived in San Francisco and proceeded to Grosse Pointe, where he was granted a fourteen day stop-over en route to the U. S. Naval Medical Center at Bethesda, Md., where he has been undergoing treat-

ment. Comdr. Zundell had suffered from beri-beri and had been reduced in weight to 105 pounds when liberated. His ill health, however, while a prisoner, worked out fortunately for him, because he was left behind as too sick to be included on the ill fated prisoners of war ship, on which the Japanese transferred some 1600 persons from Manila to Japan, the ship being sunk by United States bombs. It is not known how many of the prisoners were rescued from the sinking, but among those aboard were several friends of the Zundells, from whom no word has ever been heard. However, rumor has it that only approximately 300 of the prisoners were lost in the sinking and the rest of them are thought to have been transferred to another ship.

Lt. Comdr. William M. Silliphant, (MC), U.S.N., also an Associate of the College, was liberated at the same time from the Bilibid Hospital, a report of which was published in the April issue of this journal.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Reprints

Frank N. Allan, F.A.C.P., Boston, Mass.—1 Reprint.
J. Edward Berk, F.A.C.P., Captain, (MC), A.U.S.—1 Reprint.
Leon Bromberg, F.A.C.P., Commander, (MC), U.S.N.R.—1 Reprint.
William J. Bryan, Jr., F.A.C.P., Tulsa, Okla.—1 Reprint.
N. W. Chaikin, F.A.C.P., New York, N. Y.—1 Reprint.
James M. Flynn, F.A.C.P., Rochester, N. Y.—1 Reprint.
Hyman I. Goldstein (Associate), Camden, N. J.—1 Reprint.
Harold J. Harris, F.A.C.P., Lieutenant Commander, (MC), U.S.N.R.—3 Reprints.
Thomas A. Lebbetter, F.A.C.P., Colonel, R.C.A.M.C.—Report of the National Health Survey, Canadian Medical Procurement and Assignment Board.
Samuel Morrison, F.A.C.P., Lieutenant Colonel, (MC), A.U.S.—1 Reprint.
Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—1 Reprint.
Lawrence E. Putnam (Associate), Washington, D. C.—1 Reprint.
Leonard B. Shpiner (Associate), Captain, (MC), A.U.S.—2 Reprints.

Gifts other than by members of the College include the following:

"Diet and Disease," by Dr. C. G. McDonald, F.R.A.C.P., Sydney, Australia.

"Diet Formulary," Bureau of Medicine and Surgery, Navy Department, by Dr. George Schmitt, F.A.C.P., Farragut, Idaho.

"The Story of Penicillin, Yellow Magic," presented by Dr. Charles E. Dutchess, Medical Director of the Schenley Laboratories, New York City.

"Courage and Devotion Beyond the Call of Duty," presented by Dr. A. L. Rose, Vice President, Mead Johnson & Company, Evansville, Ind.

"Courage and Devotion Beyond the Call of Duty" is a partial record of official citations to medical officers in the United States Armed Forces during World War II. This is a preliminary edition, dated November, 1944. Among those listed are the following members of the American College of Physicians:

Colonel Otis O. Benson, Jr. (Associate), (MC), U.S.A.—Legion of Merit;
Captain Isidore Brill, F.A.C.P., (MC), A.U.S.—the Army Air Medal;
Captain John H. Chambers, F.A.C.P., (MC), U.S.N., and Capt. John M. McCants, (MC), U.S.N.—a citation for distinguished service to Mobile Hospital Unit

No. 2, at the time of the attack on Pearl Harbor, December 7, 1941, the Commanding and Executive Officers being, respectively, Captain Chambers and Captain McCants;

Lieutenant Colonel Garfield G. Duncan, F.A.C.P., (MC), A.U.S.—Legion of Merit;

Major Donald D. Flickinger (Associate), (MC), U.S.A.—Distinguished Flying Cross;

Brigadier General Leon A. Fox, F.A.C.P., (MC), U.S.A.—Distinguished Service Medal;

Colonel Dale G. Friend, F.A.C.P., (MC), A.U.S.—Legion of Merit;

Colonel James O. Gillespie, F.A.C.P., (MC), U.S.A.—Distinguished Service Medal;

Lieutenant Colonel William R. Hallaran, F.A.C.P., (MC), A.U.S.—Legion of Merit;

Commander Bartholomew W. Hogan, F.A.C.P., (MC), U.S.N.—Purple Heart;

Brigadier General Edgar Erskine Hume, F.A.C.P., (MC), U.S.A.—Oak Leaf Cluster to the Distinguished Service Medal;

Colonel Walter S. Jensen, F.A.C.P., (MC), U.S.A.—Legion of Merit;

Captain Richard A. Kern, F.A.C.P., (MC), U.S.N.R.—Letter of Commendation;

Commander William Harry Leake, F.A.C.P., (MC), U.S.N.R.—Special Citation;

Major General James C. Magee, F.A.C.P., (MC), U.S.A.—Distinguished Service Medal;

Lieutenant Edward P. McLarney, F.A.C.P., (MC), U.S.N.—Navy Cross;

Captain Alphonse McMahon, F.A.C.P., (MC), U.S.N.R.—Special Citation by Admiral Halsey;

Lieutenant Ferrall H. Moore, F.A.C.P., (MC), U.S.N.R.—Legion of Merit;

Colonel Maurice C. Pincoffs, F.A.C.P., (MC), A.U.S.—Legion of Merit;

Commander James J. Sapero (Associate), (MC), U.S.N.—Distinguished Service Medal;

Brigadier General James S. Simmons, F.A.C.P., (MC), U.S.A.—a special medal in connection with the work of the United States Typhus Commission;

Colonel Frank B. Wakemann, F.A.C.P. (MC), U.S.A.—Legion of merit, posthumously;

Captain Joel J. White, F.A.C.P., (MC), U.S.N.—Presidential Unit Citation and Legion of Merit;

Lieutenant Colonel Charles T. Young, F.A.C.P., (MC), U.S.A.—Legion of Merit.

In the book now deposited in the College Library appears the specific citation in each of the above cases.

American doctors from U. S. Military hospitals in England were among an audience of about 400 physicians and surgeons who attended a lecture on "Penicillin" by its discoverer Sir Alexander Fleming at Nottingham. The doctors were entertained to lunch by the Lord Mayor of Nottingham and the picture shows a group of Americans with the Lord Mayor, Professor Fleming and the Sheriff of Nottingham.

The Professor said America had now beaten the world in the manufacture of Penicillin by cultivating it in tanks containing scores of thousands of gallons.

Left to right: Major S. C. Meigher, 1036 Pelhamdale Ave., Pelham Manor, N. Y.; Lt. Col. L. E. McKelvey, 500 Selby Blvd., Worthington, Ohio (Colonial Hills); Capt. C. C. Chumbley, 3101 West End Ave., Nashville, Tenn.; The Lord Mayor of Nottingham; Major C. F. Vorder Bruegge, 1993 Linden Ave., Memphis 4, Tennessee; Prof. Sir Alexander Fleming; Major D. F. H. Murphey, 3235 7th Ave., No., St. Petersburg, Florida; The Sheriff of Nottingham; Lt. Col. W. A. Cooper, 333 E. 68th St., New York, N. Y.; Col. C. L. Kirkpatrick, Glencourt Apartment, Nashville, Tennessee; Lt. Col. L. S. Meriwethe, 200 Lamar Life Bldg., Jackson, Mississippi.

Left to right: Major Abramson, 60 Kilsyth Rd., Brookline, Mass.; Lt. Col. McCann, 1792 Hilcrest St., Minneapolis, Minn.; Major Lauer, 638 Arlington Place, Chicago, Illinois; The Lord Mayor of Nottingham; Major McGregor, 1809 4th Ave., N., Great Falls, Mont.; Prof. Fleming; Major Shute, New Orleans, Louisiana; Dr. Scott; Major McDouglas, Booneville, Mississippi; The Sheriff of Nottingham; Capt. Mell, 1074 Ashmount Ave., Oakland, Cal.; Major Falk, 1734 36th Ave., San Francisco, California.

Left to right: Major D. R. Kaufman, 5430 Netherland Ave., Riverdale, New York; Major F. M. Acree, 1302 Washington Ave., Greenville, Mississippi; Lt. Col. J. D. Maloney, 114 Sayles St., Lowell, Mass.; The Lord Mayor of Nottingham; Major J. J. Foley, Hartford, Connecticut; Prof. Fleming; Major G. E. Quigley, 18 Rogers St., Newton 58, Mass.; Dr. Scott; Major B. F. Thompson, Columbia, Mississippi; The Sheriff of Nottingham; Major Hyman L. Naterman, 41 Hatherly Rd., Brighton, Massachusetts; Major W. Sterling Clark, Ventura, California.

A.C.P. Postgraduate Courses

The spring Postgraduate Courses offered by the American College of Physicians were, with only a single exception, greatly oversubscribed. According to regulations of the Office of Defense Transportation, no course was allowed to exceed fifty registrants from outside of the city and environs where the Course was given. In one or two instances the total registration of courses exceeded the maximum of fifty, but only owing to the fact that the excess number came from the local city.

The Committee on Postgraduate Courses exceedingly regrets that it is not at present possible, under war conditions, to provide facilities that will fulfill the demand among physicians for these courses—in fact, we have been at present unable to accommodate all of the members of the College who desire these courses and have had to restrict the registration almost wholly to members of the College. The basic registration fee is $20 per week to members of the College; $40 per week to non-members of the College; free to medical officers of the Armed Forces.

The following table gives a summary of registration for the various courses.

Course	Associates	Fellows	Non-Members	Total	Army	Navy	U.S.P.H.S.	Civilians
No. 1	19	42	8	69	11	6	2	50
No. 2	14	23	0	37	4	0	1	32
No. 3	9	20	16	45	8	0	4	33
No. 4	14	35	1	50	7	1	0	42
No. 5	6	24	0	30	4	0	0	26

Course No. 1, CARDIOLOGY, Columbia University College of Physicians and Surgeons, New York; March 19–24, 1945.

Course No. 2, MECHANICS OF DISEASE, Harvard Medical School and Peter Bent Brigham Hospital, Boston; April 9–21, 1945.

Course No. 3, CLINICAL MEDICINE WITH SPECIAL EMPHASIS UPON THE HEMATOLOGIC VIEWPOINT, Ohio State University College of Medicine, Columbus; April 16–21, 1945.

Course No. 4, GASTRO-INTESTINAL DISEASES, Graduate Hospital, University of Pennsylvania, Philadelphia; April 23–28, 1945.

Course No. 5, APPLICATIONS OF PSYCHIATRY TO THE PRACTICE OF INTERNAL MEDICINE, University of Wisconsin Medical School, Madison; April 30–May 5, 1945.

Autumn, 1945, Courses. Interested readers should watch these columns in succeeding numbers for announcements concerning the Autumn Schedule of Courses. Members are encouraged to send in suggestions to the Executive Offices of the College.

The Committee on Postgraduate Courses and the Board of Regents will arrange several courses during October, November and December. At this time definite arrangements have been made for the repetition of the course in CARDIOLOGY under the Directorship of Dr. Paul D. White at the Massachusetts General Hospital, Boston, during the week of November 5, 1945.

REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U. S. ARMY

Colonel William C. Menninger, F.A.C.P., Chief Consultant in Psychiatry to the Surgeon General, was the featured speaker at the Mental Health in Wartime forum, the first of a series to be held by the Washington (D.C.) Metropolitan Health Council. He stressed the fact that the neuropsychiatric service in the Army provides not only treatment opportunities but preventive measures. He expressed the hope that popular understanding of psychiatry would "definitely dispel the clouds of mystery and the irrational stigmatization of those afflicted with emotional illness and bring about a public demand for the application of psychiatric principles to our legal, our educational, our political and our medical practices."

During March a glider service was inaugurated in the European Theater to evacuate our wounded from Remagen. Observers reported that the shock incident to being "snatched" into the air was absorbed by an improved towing device. It is now possible that gliders may almost eliminate ambulances for hauling our battle casualties long distances over shell torn roads, giving them a faster, smoother ride to the hospital. The gliders serve a dual purpose. Coming into the battle area they can carry twelve litter patients or nineteen walking wounded. Ambulance gliders were first used experimentally by the British in Burma and New Guinea.

Advancements in Rank

From Major to Lieutenant Colonel:

Thomas Hale Ham, F.A.C.P., Brookline, Mass.
Joe Hollis Little, F.A.C.P., Mobile, Ala.
Winthrop Wetherbee, Jr., F.A.C.P., Boston, Mass.

From Captain to Major:

Marvin R. Corlette, F.A.C.P., Pasadena, Calif.

National Foundation for Infantile Paralysis Scholarships

Scholarships for training in physical therapy under the $1,267,600 program of the National Foundation for Infantile Paralysis are available immediately for classes commencing in June and July, according to Basil O'Connor, President of the Foundation. These scholarships are for nine to twelve months courses in private schools of physical therapy. The scholarships will cover tuition and maintenance in accordance with the student's needs.

The training program will be carried out with the assistance of a special committee under the chairmanship of Dr. Irvin Abell, Louisville, Ky. Candidates must have two years of College, including biology and other basic sciences, or be graduates of accredited schools of nursing or physical education. Applications should be made to the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y., or to the American Physiotherapy Association, 1790 Broadway, New York 19, N. Y.

Under the personal direction of Dr. Louis N. Katz, F.A.C.P., Director of Cardiovascular Research, the annual intensive two weeks course in electrocardiography for graduate physicians will be given at Michael Reese Hospital, Chicago, August 20 to September 1, 1945. Group and individual instruction will be given; the course is open to beginning and advanced students in electrocardiography.

Lieutenant Commander Howard G. Bruenn, (MC), U.S.N.R., F.A.C.P., was the Navy physician assigned to look after the late President, Franklin Delano Roosevelt, during his stay at Warm Springs, where he died on April 12. According to radio announcements, Dr. James E. Paullin, F.A.C.P., former President of the American College of Physicians, Atlanta, was immediately called in consultation at the time of the President's collapse.

Dr. Elmer L. Sevringhaus, F.A.C.P., Professor of Medicine at the University of Wisconsin Medical School and College Governor for the State of Wisconsin, is absent from this country for several months on a special mission to Italy.

Retiring Medical Officer, U. S. Army, Seeks Appointment

A Fellow of the American College of Physicians, born in 1882, has been retired for age as Colonel in the Medical Corps of the Regular Army. He is immediately available for an appointment, preferably in the East. He has had wide experience in public speaking and in liaison work with the public and with the general medical profession. He is well prepared to teach preventive medicine or tropical medicine, but is also interested in administrative work in connection with a medical school, medical society, or departments of health. He attended Wesleyan University for three years and graduated in medicine from Columbia University College of Physicians and Surgeons in 1908. He graduated from the Army Medical School in Washington in 1912 and has had the usual Army career, with assignments at Army installations all over the United States, Panama, Hawaii, the Philippines and elsewhere. He has published several worthy papers, is in exceptionally good health and of keen mental capacities.

The College by acting as an intermediator will be performing a valuable service to this Fellow, as well as to any institution through which an appointment may develop. Address the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

Dr. William Harvey Perkins, F.A.C.P., Dean of Jefferson Medical College of Philadelphia, will receive the honorary degree of Doctor of Science at the June commencement exercises of Dickinson College.

Colonel Maurice C. Pincoffs, (MC), A.U.S., F.A.C.P., who has served almost from the beginning of the war as Consultant in Medicine for the Pacific Theater, has been made Public Health Administrator for the City of Manila. His address is Advanced Detachment Headquarters, U.S.A.F.F.E, A.P.O 501, c/o Postmaster, San Francisco, Calif.

Brigadier General Hugh J. Morgan, F.A.C.P., Consultant to the Surgeon General of the U. S. Army, has been touring the European War Theater. According to the lay press of April 7, General Morgan had an audience with Pope Pius in Vatican City.

Dr. Russell S. Boles, F.A.C.P., was recently reëlected President of the Medical Board of the Philadelphia General Hospital, this being his third consecutive year.

The Sugar Research Foundation announced on April 16, 1945, six grants to scientists for research into new industrial and nutritional uses for sugar. The awards amount to $45,400, bringing to more than $300,000 the total funds which the Foundation has made available to science. One of the grants, $2500 for one year, to study further the body's relative rate of absorption of sucrose, dextrose and levulose, was made to Dr. I. M. Rabinowitch, F.A.C.P., of McGill University Faculty of Medicine, Montreal.

Dr. Christopher G. Parnall, Sr., F.A.C.P., for the past twenty-one years Medical Director of Rochester General Hospital, has resigned, effective October 1. Dr. Parnall will devote his time to consultation in hospital planning and construction, a work in which he has been engaged for the past thirty years. He has been retained as consultant on several large projects costing several millions of dollars. His most recent assignment was that of director of the technical staff for the Dewey Commission which investigated the care of the mentally ill in the State of New York.

Dr. H. Vernon Madsen (Associate) has completed his work at the Henry Ford Hospital, Detroit, and has opened an office for practice at 525 Sycamore Street, Waterloo, Iowa. He will give special attention to diseases of the chest.

Dr. Franklin C. Cassidy, F.A.C.P., formerly stationed at the Veterans Administration, Walla Walla, Washington, as Clinical Director, has been promoted and transferred to the Veterans Administration, Waukesha, Wisconsin, as Manager.

Dr. Eugene P. Pendergrass, F.A.C.P., is Chairman of the Board of Chancellors of the American College of Radiology. Under his leadership the College has carried on an alert and an aggressive program that has accomplished and is accomplishing some definitely desirable results. Dr. Pendergrass' statement, published in a recent bulletin of the College, would be worthy of any organization, "our fullest devotion in time, effort and serious study will be demanded in the critical years ahead if we are to fulfill the obligations we have assumed for the protection of our specialty and the improvement of service in the care of the sick."

A considerable number of physicians are Fellows of both the American College of Radiology and the American College of Physicians; hence this brief report will be of specific interest to many and of general interest to all. The American College of Radiology has the following problems of particular importance under consideration at present: Radiology in prepayment plans; extension of facilities for training residents in radiology; the maintenance of proper standards in the relations between radiologists and hospitals; malpractice insurance; inspection of hospital x-ray departments; the distribution of radiological service.

It is interesting to note that the Annual dues of Fellows of the American College of Radiology are at present $25 per annum, with a prospect of materially increasing the amount in the future. Fellowship dues in the American College of Physicians are $15 per annum, with certain reductions therefrom for full-time teachers, laboratory and research workers, with full waiver of dues during the war to medical officers on active military duty.

The American College of Radiology will coöperate with other existing groups in national post-war planning for medical service, but it will, furthermore, have its own individual program for taking care of its own members, following discharge from military service. Its Commission on Education is undertaking a study of this matter and plans are under way for the preparation of a "Manual of Graduate Training" for the use of hospitals and radiologists who have not heretofore trained residents. Plans will also be completed for a series of short postgraduate Courses to be conducted in various sections of the country during the next few years.

Oral Examinations, American Board of Internal Medicine

Oral examinations will be held during 1945 in accordance with the following schedule. Candidates who have been advised of the successful completion of the written examination will be accepted.

(1) Philadelphia, Pa., June 6–7–8. For candidates from Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia. (Closing date, May 5.)

(2) New Orleans, La., May 21–22–23. For candidates from Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Oklahoma, Tennessee, Texas. (Closing date, May 5.)

(3) Chicago, Ill., June 27–28–29. For candidates from Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin. (Closing date, May 12).

(4) San Francisco, Calif., Oct. 15–16–17. For candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming. (Closing date, Sept. 1).

Candidates who have been notified of the approval of their applications for admission to an oral examination in a subspecialty will be admitted at the time and place of the oral examination in internal medicine, provided the oral examination in internal medicine is satisfactory.

Candidates with an A.P.O. or Fleet P.O. address who find it possible to report, please advise the central office of the Board as to the most convenient place on the schedule. The Board will make every effort to meet their convenience.

The Board will appreciate your consideration if you will not request admission unless you are reasonably sure of being present. The schedule must of necessity be fixed within geographical limits, but will be sufficiently flexible to accommodate candidates in the armed forces if they have a change of station after the closing date for the acceptance of applications.

Candidates previously certified in Internal Medicine will be admitted to oral examination in their subspecialty in accordance with the above schedule if application has been approved and notification has been received.

Write immediately for application form to the American Board of Internal Medicine, 1301 University Ave., Madison 5, Wis. (Editor's Note: The above notice received for publication on April 16, 1945, too late for inclusion in the April issue of this journal.)

Dr. Samuel M. Poindexter, F.A.C.P., Boise, College Governor for Idaho, was recently reappointed a member of the State Board of Medical Examiners.

Dr. Theodore R. Van Dellen, F.A.C.P., has been appointed health editor of the Chicago *Tribune*.

Dr. William J. Mallory, F.A.C.P., Washington, is one of a committee of three who have recently completed the writing of the history of the Medical Society of the District of Columbia.

Dr. William M. LeFevre, F.A.C.P., was recently appointed a member of the Muskegon (Mich.) Board of Health.

Dr. Raymond Hussey, F.A.C.P., Detroit, is dean of the School of Occupational Health and professor of preventive medicine at Wayne University College of Medicine.

Col. James E. Ash, F.A.C.P., Director of the Army Institute of Pathology, Washington, delivered the tenth Harrison S. Martland Lecture at the Newark (N. J.) Academy of Medicine, March 28, on "The Army Institute of Pathology and Its Contribution to the Study of Diseases Prevalent in the Military Air Group."

The William Freeman Snow Medal for distinguished service to humanity was awarded to Major General Merritte W. Ireland, F.A.C.P., at the 32nd annual meeting of the American Social Hygiene Association at Chicago recently. General Ireland was a former Surgeon General of the U. S. Army.

Recently Col. John B. Youmans, F.A.C.P., Director of the Nutrition Division of the Medical Corps of the U. S. Army, addressed the University of Virginia chapter of Alpha Omega Alpha on "Principles Underlying the Early Diagnosis of Nutritional Deficiency Disease."

A Symposium on Industrial Medicine was conducted at the New York Post-Graduate Medical School, April 2–6, under the direction of Dr. Harry J. Johnson, F.A.C.P., and Dr. Frank R. Ferlaino. Among those on the faculty were: Dr. C. Charles Burlingame, F.A.C.P.; Dr. Maurice Bruger, F.A.C.P.; Dr. Charles A. Poindexter, F.A.C.P.; Dr. A. Wilbur Duryee, F.A.C.P.; Dr. Dwight O'Hara, F.A.C.P.; and Dr. John D. Currence, F.A.C.P.

Dr. Hubert M. English, F.A.C.P., has been elected president of the Gary (Ind.) Board of Health.

Dr. J. C. Geiger, F.A.C.P., San Francisco, was recently notified by the Consul General of Portugal, Euclides Goulart da Costa, that the Portuguese Government

and its Premier Salazar have conceded to him the most ancient and revered European and Catholic order, the Cavaleiro da Ordem de Cristo (Order of Christ), with the following citation: "For great personal and professional merit in public health, and for important services to the Portuguese people of Portugal and of California."

Dr. Frank H. Krusen, F.A.C.P., head of the section on physical medicine, Mayo Clinic, Rochester, and Dr. George Morris Piersol, F.A.C.P., director of the division of physical medicine, University of Pennsylvania, Philadelphia, gave two of the three lectures of a course in physical medicine sponsored by the District of Columbia Medical Society during April, their subjects being, respectively, "The Future of Physical Medicine" and "Clinical Aspects of Physical Medicine."

The Charles V. Chapin Memorial Award of the Rhode Island Medical Society was made to Dr. Reginald Fitz, F.A.C.P., Boston, on February 5. Dr. Fitz delivered the Chapin Oration during the meeting of the Rhode Island Medical Society in May 1944, but the medal was not ready at that time and was formally presented on the date first referred to.

Dr. Tom D. Spies, F.A.C.P., assistant professor of medicine, University of Cincinnati College of Medicine, gave the first Edward H. Cary Lecture at the Southwestern Medical College of the Southwestern Medical Foundation, Dallas. This lectureship was established as an expression of appreciation to Dr. Edward H. Cary, president of the Foundation, for his work in connection with the Foundation and the Medical School.

Dr. Warfield T. Longcope, F.A.C.P., Baltimore, is a vice president of the American Association for the Advancement of Science, representing the field of medical science. Dr. Anton J. Carlson, F.A.C.P., Chicago, has recently retired as president.

The Long Island College of Medicine, Brooklyn, and the Medical Society of the County of Kings, through a joint committee on postgraduate education, are offering numerous postgraduate courses for local physicians. Most of the courses began during April and will be continued for terms varying from 8 to 16 sessions, 1 or 2 meetings per week.

Among courses listed are the following: ALLERGY, Dr. George A. Merrill, F.A.C.P., Director; ARTHRITIS, Dr. A. S. Gordon, F.A.C.P., Director; ELECTROCARDIOGRAPHY, Dr. S. R. Slater, F.A.C.P., Director; ELECTROCARDIOGRAPHY AND CLINICAL CARDIOLOGY, Dr. Charles Shookhoff, F.A.C.P., Director; GASTROENTEROLOGY, Dr. Benjamin M. Bernstein, F.A.C.P., Director; CLINICAL HEMATOLOGY, Dr. Maurice Morrison, F.A.C.P., Director; HYPERTENSION AND NEPHRITIS, Dr. Harry Mandelbaum, F.A.C.P., Director; CLINICAL PEDIATRICS, Dr. Abraham M. Litvak, F.A.C.P., Director; ENDOCRINE DISEASES AND DISORDERS IN CHILDREN AND ADOLESCENTS, Dr. Maurry B. Gordon, F.A.C.P., Director; PATHOLOGY OF INTERNAL MEDICINE, Dr. Jacob M. Ravid, F.A.C.P., Director.

Dr. A. C. Ivy, F.A.C.P., Chicago, has been appointed for a three year term to membership on the National Advisory Cancer Council of the U. S. Public Health Service.

Dr. George E. Wakerlin, F.A.C.P., Chicago, has been elected chairman of the Chicago Cancer Committee.

Dr. Wakerlin has been appointed assistant dean in charge of teaching and research at the Rush-Presbyterian Hospital, a division of the University of Illinois College of Medicine.

Captain Vincent Hernandez (Associate), (MC), U.S.N., was recently awarded the Bronze Star, "for meritorious achievement as force medical officer on the staff of Commander Air Force, United States Atlantic Fleet, from June 1943 until January 1945. Skilfully coördinating the work of medical officers of the Air Force, Atlantic Fleet, with that of naval air stations basing fleet aviation units, Captain Hernandez organized and supervised the activities of the officers under his jurisdiction and, by his untiring efforts and painstaking attention to particular needs, effected measures to insure the physical fitness, endurance and resistance of flying and maintenance personnel engaged in the widespread battle of the Atlantic. His exceptional success in this vital service reflects the highest credit on Captain Hernandez and the United States Naval Service."

The late Dr. Logan Clendening, F.A.C.P., left a bequest of $50,000 to the University of Kansas Endowment Association to be used for the Department of Medical History.

The New York Academy of Medicine will conduct its Eighteenth Graduate Fortnight October 8–19. The general theme will be "Contributions of the War Effort to Medicine."

Dr. Roger S. Mitchell, Jr., F.A.C.P., of Glens Falls, New York, retired from active duty as Major, (MC), A.U.S., on May 4, 1945, and plans to work at the North Carolina Sanatorium, Sanatorium, N. C., starting June 1, continuing until he has regained his health.

The American College of Chest Physicians, with a membership in 23 countries, has cancelled its annual meeting scheduled to be held at Philadelphia, June, 1945.

The Executive Council of the College voted to hold a business meeting of the Board of Regents at Chicago, June 17.

As the result of a nationwide poll among leaders in medical science, Dr. Edwin J. Cohn, Professor of Biochemistry at Harvard University, has been chosen as the first winner of The Passano Foundation award. Presentation of the $5,000 cash award will be made at an appropriate ceremony in historic Osler Hall of the Medical and Chirurgical Faculty of Maryland, in Baltimore, on the night of May 16.

The Foundation, which was established in 1944 by The Williams and Wilkins Company, Medical Publishers, of Baltimore, proposes to aid in any way possible the advancement of medical research, especially research that bears promise of clinical application. For the encouragement of such research the Foundation has established the award as one of its activities.

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School; Dr. Nicholson J. Eastman, Professor of Obstetrics in the Johns Hopkins University Medical School; Dr. George W. Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington, represent the medical profession on the Board of Directors of The Foundation.

Dr. Cohn is distinguished for his work on the fractionation of blood. Beginning in 1919 with a study of blood and blood proteins, Dr. Cohn's research has progressed until it has yielded a spectacular group of five principal fractions of blood plasma which hold untold promise of usefulness in medical science.

Fraction I contains fibrinogen, a substance which forms blood clots when activated by thrombin and from which a series of fibrinogen plastics can be made and fashioned into any shape and to any consistency from elastic to solid. Because this plastic material can be absorbed in the body it has many potential uses in surgery.

Fraction II contains immune globulin, which is useful in establishing an immunity in such virus diseases as measles.

Fractions III and IV are proteins whose functions and usefulness have not yet been fully exploited, while fraction V contains the plasma albumin proteins which give the plasma its property of combating shock.

Following the presentation of the award by Mr. Edward B. Passano, Chairman of the Board of The Williams and Wilkins Company, Dr. Cohn will read a paper concerning the applications of his work on blood plasma to the field of clinical medicine.

The War-Time Graduate Medical Meetings

This joint effort by the American College of Surgeons, the American Medical Association and the American College of Physicians has been quietly and efficiently going forward almost from the first of the War—a program of graduate lectures, demonstrations, ward teaching carried to physicians in Army and Navy installations in all parts of this country. Hundreds of authorities, teachers and practitioners, in the many subdivisions of medicine have been and still are giving their time unstintingly to this worthy work. Enough credit and acknowledgment have not been given either to the faculties or to the many Zone chairmen and committeemen. Let us not forget the fine work the War-Time Graduate Medical Committee (Dr. F. F. Borzell, Chairman, Dr. Alford Blalock and Dr. George Morris Piersol) and its Zone Committees and faculties are doing.

As but one example of the activity of a Zone Committee, District No. 14, embracing Illinois, Indiana and Wisconsin, of which Dr. W. O. Thompson, F.A.C.P., Chicago, is the Chairman, during April alone conducted thirty-four separate sessions with repeated programs, in some instances, at the Billings General Hospital, Wakeman General Hospital, Gardiner General Hospital, Fort Sheridan, Vaughan General Hospital, Great Lakes Naval Hospital, Mayo General Hospital, Camp Ellis, Chanute Field, Camp McCoy, Truax Field, Fort Knox and Nichols General Hospital.

Following appear some of the programs scheduled for the immediate future:

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Induction Center, Grand Central Palace, New York, New York

May 18 Deleterious Effects of Drugs on the Hemopoietic System—Dr. Nathan Rosenthal.

May 25 Deficiency States and Their Recognition—Dr. H. D. Kruse.

Region No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

May 18 Health Department Military Liaison in Venereal Disease—Dr. Norman Ingraham.

Region No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. C. B. Conklin.

Newton D. Baker General Hospital, Martinsburg, West Virginia

May 21 Narcosynthesis and Hypnosis—Dr. Addison McGuire Duval.
Peripheral Vascular Diseases Due to War-Time Conditions—Dr. J. Ross Veal.
June 4 Chest Injuries in War—Dr. I. A. Bigger.
Shock—Dr. E. I. Evans.
June 18 Liver Diseases Seen in the Present War—Colonel Balduin Lucke.

A.A.F. Regional Hospital, Langley Field, Virginia

May 25 Aviation Medicine—Dr. L. G. Lederer.
Fundamentals of Plastic Surgery—Dr. Robert E. Moran.
June 29 Gastro-enterology—Dr. Lay Martin.
Traumatic Surgery of the Abdomen—Lieutenant R. C. Wood.

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Gardiner General Hospital, Chicago, Illinois

May 16 Mental Hygiene and the Prevention of Neuroses in War.
May 23 Wound Healing and Tendon Surgery.
June 6 Peptic Ulcer, Gall Bladder and Liver Diseases.
June 13 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
June 20 Chest Diseases and Diseases of the Larynx.
June 27 Low Back Pain.

Station Hospital, Fort Sheridan, Illinois

May 16 Peptic Ulcer, Gall Bladder and Liver Diseases.
May 23 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
June 6 Chest Diseases and Diseases of the Larynx.
June 13 Low Back Pain.
June 20 Heart Disease and Allied Conditions.
June 27 Bone and Joint Infections.

Mayo General Hospital, Galesburg, Illinois

May 16 Chest Diseases and Diseases of the Larynx.
May 23 Low Back Pain.
June 6 Heart Disease and Allied Conditions.
June 13 Bone and Joint Infections.
June 20 Arterial Vascular Disease—Traumatic Lesions.
June 27 Repair of Bone in Fractures and Diseases.

Vaughan General Hospital, Hines, Illinois

May 16 Heart Disease and Allied Conditions.
May 23 Bone and Joint Infections.
June 6 Arterial Vascular Disease—Traumatic Lesions.
June 13 Repair of Bone In Fractures and Diseases.
June 20 Diseases of the Kidneys—Urogenital Tract.
June 27 Blood Dyscrasias, Malaria, Filariasis.

Station Hospital, Camp Ellis, Illinois

May 16 Arterial Vascular Disease—Traumatic Lesions.
May 23 Repair of Bone in Fractures and Diseases.
June 6 Diseases of the Kidneys—Urogenital Tract.
June 13 Blood Dyscrasias, Malaria, Filariasis.
June 20 High Blood Pressure.
June 27 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.

Station Hospital, Camp McCoy, Wisconsin

May 16 Diseases of the Kidneys—Urogenital Tract.
May 23 Blood Dyscrasias—Malaria—Filariasis.
June 6 High Blood Pressure.
June 13 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
June 20 Conditions Affecting Glucose Metabolism.
June 27 Brain and Spinal Cord Injuries.

Station Hospital, Truax Field, Wisconsin

May 16 Conditions Affecting Glucose Metabolism.
May 23 Brain and Spinal Cord Injuries.
June 6 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care.
June 13 Plexus and Peripheral Nerve Injuries.
June 20 Dermatological Diseases.
June 27 Burns and Plastic Surgery.

Station Hospital, Chanute Field, Illinois

May 16 Dermatological Diseases.
May 23 Burns and Plastic Surgery.
June 6 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment.
June 13 Endocrinology.
June 20 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
June 27 Psychosomatic Medicine.

Billings General Hospital, Indiana

May 16 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment.
May 23 Endocrinology.
June 6 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
June 13 Psychosomatic Medicine.
June 20 Wound Healing and Tendon Surgery.
June 27 Mental Hygiene and the Prevention of Neuroses in War.

Wakeman General Hospital, Indiana

May 16 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
May 23 Psychosomatic Medicine.
June 6 Wound Healing and Tendon Surgery.

June 13 Mental Hygiene and the Prevention of Neuroses in War.
June 20 Thrombosis, Thromboplebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
June 27 Peptic Ulcer, Gall Bladder and Liver Diseases.

REGION No. 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr. F. D. Dickson, Chairman; Dr. O. P. J. Falk, Dr. H. H. Turner.

A. A. F. Regional Hospital, Smoky Hill Army Air Field, Salina, Kansas

June 14 Gastrointestinal (X-Ray Findings in Abdominal Pathology)—Dr. Ira H. Lockwood.
Shock, Burns and Blood Derivatives—Dr. Vincent T. Williams.

REGION No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

Hammond General Hospital, Modesto, California

May 30 Laboratory Aids in the Diagnosis of Disease—Dr. Jesse Carr.
June 13 Subacute Bacterial Endocarditis—Dr. William J. Kerr.

Station Hospital, Hamilton Field, California

May 16 Fractures of the Extremities—Dr. Carl Anderson.
May 30 Diagnosis and Treatment of Arthritis—Dr. Stacy R. Mettier.

Station Hospital, Camp Roberts, California

May 19 Diagnosis and Treatment of Arthritis—Dr. Hans Waine.
May 26 The Treatment of Poliomyelitis—Dr. Henry D. Brainerd
June 16 Severe Infections of the Hand—Dr. Edmond D. Butler.

Station Hospital, Stockton Army Air Base, California

May 16 The Treatment of Syphilis—Dr. Norman N. Epstein.
May 30 Use and Misuse of Endocrine Preparations—Dr. Ernest W. Page.
June 13 Early Ambulation of Surgical Patients—Dr. H. Glenn Bell.
June 20 Diagnosis and Treatment of Arthritis—Dr. Hans Waine.
June 27 Injuries to the Knee Joint—Dr. Carl E. Anderson.

Oakland Area Station Hospital, Oakland, California

May 23 Diagnosis and Treatment of Hemorrhagic States—Dr. Paul M. Aggeler.

OBITUARIES

DR. WILLIAM M. DONALD

Dr. William M. Donald, Fellow of the American College of Physicians since 1917, was born in Allonburg, Ontario, Canada, in the year 1860. After completing one year at the University of Toronto, he entered McGill University Faculty of Medicine which he attended for two years, transferring to Wayne University College of Medicine, where he received his medical degree in 1887.

For many years Dr. Donald was Professor of Internal Medicine at Wayne University College of Medicine. At one time he was Chief of Staff and Attending Physician at St. Mary's Hospital. In later years he was Consultant in Internal Medicine at the Evangelical Deaconess Hospital and Jefferson Clinic. He was President of the Wayne County Medical Society from 1922 to 1923; President of the Tri-State Medical Association in 1928; former President of the Michigan Health Exposition; Emeritus Member of the Michigan State Medical Society, having served at one time as Chairman of its Medical Section. He served as Chairman of the Wayne County Board of Review during World War I. He received an Honorary Degree of Doctor of Science in Medicine from Wayne University in 1935.

Keenly interested in the science of art, literature and philosophy, Dr. Donald established the "Doctors Corner" of the Detroit Public Library, where he gathered many volumes written by physicians on non-medical subjects and fiction.

His inspiring personality, enthusiasm and leadership were demonstrated in his untiring efforts given to the Protestant Children's Home of Detroit for more than thirty years.

His traits of honesty, kindness, charity and determination which shone throughout his life were dimmed only by his death in Grace Hospital, Detroit, December 20, 1944. The Michigan Fellows and Associates of the American College of Physicians join his family and many friends in mourning the passing of this eminent physician.

Dr. Donald leaves his son, Lt. Colonel Douglas Donald, who served as Governor for the American College of Physicians in Michigan until he was commissioned in the United States Army in 1942, and is now chief of medicine of the 40th Station Hospital in Corsica. A daughter, Mrs. Hendriek Pieter Van Gelder of Toronto, Canada, also survives.

P. L. LEDWIDGE, M.D.,
Acting Governor for the State of Michigan

DR. WILLIAM NORTHRUP

Dr. William Northrup, Fellow of the American College of Physicians since 1919, was born in Elgin County, Ontario, in 1866. He attended

Trinity Medical College, Toronto, and later received his medical degree from the University of Western Ontario Medical School in London in 1894. He continued his education with postgraduate study at Rush Medical College, Chicago, in Edinburgh, Scotland; London, England; and Breslau, Germany. He later did postgraduate work at the Trudeau School for Advanced Study of Tuberculosis, Saranac Lake, New York.

Dr. Northrup was former President of the Kent County Medical Society; Physician to Michigan State Reformatory, Ionia. He was on the Consulting Staff of Butterworth, St. Mary's and Blodgett Memorial Hospitals, and he was a member of the American Medical Association.

After a long and fruitful life, Dr. Northrup died in Grand Rapids, Michigan, December 9, 1944, at the age of seventy-seven.

P. L. LEDWIDGE, M.D., F.A.C.P.,
Acting Governor for the State of Michigan

DR. JOHN WILLIAM FLINN

Dr. John William Flinn, F.A.C.P., Prescott, Arizona, died November 21, 1944, aged 74, of carcinoma of the rectum.

Dr. Flinn was born at Wallace, Nova Scotia, July 10, 1870. On his father's side he was descended from Manxmen, his grandfather having come to Canada from the Isle of Man. His mother's people came to Canada from Scotland. He attended Pictou Academy, and received his medical education at McGill University, Montreal, graduating in 1895. Thereupon he returned to his home town and engaged in general practice until 1898, when he was forced to change climate because of chronic pulmonary tuberculosis from which he had suffered for some time. He came to Arizona, locating in Kingman in September, 1898, where he continued in general practice until 1902, in which year he removed to Prescott. Shortly after his arrival in Prescott he became ill with tuberculous pneumonia which confined him to bed for six months or more. Following recovery Dr. Flinn in 1903 established the Pamsetgaaf Sanatorium. Having been impressed by Osler's dictum regarding tuberculosis, namely, that one should have "pure air, maximum sunshine, equable temperature," he took the first letters of these words and added "good accommodation and food," creating the name "Pamsetgaaf." This sanatorium was the pioneer institution of its sort west of the Mississippi, and here Dr. Flinn carried on his clinical and research work in tuberculosis during the next forty years, continuing as its medical director to the time of his death.

During these four decades of fruitful research and treatment of tuberculosis, Dr. Flinn saw many changes in the concepts regarding the disease, several of which he was instrumental in bringing about. While not a prolific writer, he was a constant reader and keen observer of the work of others, a severe critic of his own practice, the results of which he kept a detailed record, and from time to time he presented carefully prepared papers,

always eagerly received and listened to with respect by his confreres at home and abroad.

Because of his own pulmonary condition, Dr. Flinn was forced to spend each afternoon at bed-rest, and he became a great student of the literature on tuberculous and other lung diseases. Throughout his whole medical life, in spite of physical handicaps, Dr. Flinn gave generously of his time and strength to organized medicine. One of the "famous fighting four" of Yavapai County, he was always in the forefront of any constructive activity of his own county medical society or his state organization. He was made secretary of the Arizona State Medical Association in 1908 and served through 1911, when he was forced to relinquish this office because of physical limitations. He was unanimously elected president of the Association in 1914.

Dr. Flinn had three sons and two daughters. Dr. Zebud M. Flinn, an Associate of the American College of Physicians, was killed in the Panama Canal Zone in 1940. Dr. Robert S. Flinn, like his father, is a Fellow of the College, and the third son, John S. Flinn, is serving as a Captain in the Army of the United States.

Dr. John Flinn—a brave warrior, a good friend, a useful citizen, a worthy and respected confrere—we who remain glory in your achievement and will ever cherish your memory.

Selected from an Obituary prepared by
Dr. W. Warner Watkins, F.A.C.P., Phoenix

DR. HARLAN PAGE MILLS

With the passing of Dr. Harlan Page Mills, F.A.C.P., Phoenix, on February 27, 1945, at the age of 72, the pioneer pathologist in Arizona laid down his work and went to his reward.

Dr. Mills was born in Worth County, Missouri, August 29, 1873. He attended Maryville (Mo.) Seminary and Missouri Wesleyan College, thereafter receiving his medical degree from the Marion Sims Beaumont College of Medicine in 1902. He served his internship at the Ensworth Hospital, St. Joseph, Mo. He entered general practice at Sheridan, Mo., where he remained for several years. In 1909 he accepted the position of assistant physician at the Missouri State Hospital No. 2, St. Joseph, and was later advanced to pathologist, in which position he served until moving to Phoenix. During this time, in conjunction with another member of the staff, he published the report of a remarkable case which gained wide publicity as "a human hardware store" (J.A.M.A., Jan. 21, 1911). This patient, a woman, was found at necropsy to have 1446 different articles of hardware in her stomach, including teaspoons, dozens of nails, tacks, pins, and so forth.

In 1914 Dr. Mills became pathologist and assistant psychiatrist at the Arizona State Hospital. In 1917 he became associated with the Pathological Laboratory, then a young and struggling venture. His work in

and with that organization and its affiliation with the two general hospitals in Phoenix, along with St. Luke's Home, made up the circle of activities in which Dr. Mills spent the remainder of his professional life. Shortly after becoming associated with the Pathological Laboratory, Dr. Mills started clinical laboratory work at St. Joseph's Hospital in Phoenix, at first bringing all specimens to his office, and later doing the examinations in the hospital with his own microscope which he carried back and forth. From this humble start, the laboratory department of this hospital expanded until it reached such proportions that a full-time pathologist was required. The same development took place at the Good Samaritan Hospital—then known as the Arizona Deaconess Hospital—where clinical laboratory work was started on a shoestring and developed through the years until it too required the services of a full-time clinical pathologist. Dr. Mills was made consulting pathologist for each institution upon his retirement from the active direction of their pathologic departments. He was also made an honorary member of the staff of each hospital, in recognition of his more than twenty-five years of service as head of their respective departments.

Dr. Mills held membership in the Maricopa County Medical Society (President, 1920), the Arizona Medical Association, Southwestern Medical Association, Radiological Society of North America (formerly a counselor), and he was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931. He was a Diplomate of the American Board of Pathology. He was a member of the Kiwanis Club, the Arizona Club, and the Phoenix Chamber of Commerce. Outside of his professional work, his interest was in quiet cultural pursuits, his home with its flowers and shrubbery, music and reading, and a citrus grove in which he took considerable pride.

It should be recorded that Dr. Mills was known almost as well in the specialty of radiology as in that of pathology. While not a prolific writer he did produce personally or in collaboration with others some eighteen published articles, which reflect his interest in the unusual and his careful study of useful clinical laboratory procedures.

His physical disability was cardiovascular, arising from an arteriosclerosis of obliterating type. He had suffered a sudden attack of Menier's disease with resulting deafness some years ago. Later a sudden paralysis of the left diaphragm developed; arteries in one or more fingers closed, causing painful Buerger's syndromes. A finger was amputated and histologic study revealed the characteristic endarteritis obliterans. Doubtless similar arterial occlusions brought on the final fatal illness, which culminated in decompensation and pulmonary edema.

Dr. Mills won the respect of his wide circle of friends, this respect growing into an abiding affection on the part of those who were closely associated with him in professional work or social contacts. Through the years his poise and courtesy, his consideration for others, his attention to detail and his excellent judgment in his work, his cultural appreciation of music, art

and literature, marked him as a Christian gentleman, a scientist of no mean achievement, a sympathetic friend.

Selected from an Obituary prepared by
Dr. W. Warner Watkins, F.A.C.P., Phoenix

DR. FRANK GRAUER

Dr. Frank Grauer, F.A.C.P., one of the oldest active physicians in the City of New York, died in the Presbyterian Hospital of New York City of a coronary occlusion on February 16, 1945.

Dr. Grauer was born in New York, February 25, 1864, attended the College of the City of New York, and graduated from the Bellevue Hospital Medical College in 1884. During his early career he was assistant to the chair of pathological anatomy and medicine, and instructor in the Carnegie Laboratory of Bellevue Hospital Medical College; curator to Bellevue Hospital; pathologist to the Harlem, City, St. John's Guild, and Park Hospitals; also, formerly physician and pathologist to the Lutheran Hospital of Manhattan. Following his graduation he did postgraduate work in the University of Berlin and in Frankfurt, Germany, and later studied at Harvard and Johns Hopkins.

Dr. Grauer was held in very high regard as a doctor, and it is of interest to note that his Fellowship was sponsored by the late Drs. Lewellys F. Barker, Harold Brooks, and Joseph H. Byrne who was Associate Secretary General of the College from 1918 to 1921. Dr. Grauer continued to look after his practice until a short time before his death.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. GUSTAV ADOLPH PUDOR

Dr. Gustav Adolph Pudor, F.A.C.P., Portland, Maine, died March 7, 1945. He was born in Portland, August 31, 1864. His father Dr. Christian F. Pudor died when the boy was barely 6 years old, and his education was guided by his mother. He attended the public schools and entered Harvard College, graduating with the degree of Bachelor of Arts in 1886 summa cum. He then entered Harvard Medical School and received his medical degree in 1889. Two years of study in Berlin University followed, where in the latter part he had a severe attack of the then rampant influenza which nearly cost him his life, as he insisted on continuing his studies until he broke down, and only complete and protracted rest in a quiet small town preserved his life. In 1890 the young doctor hung out his shingle at the door where his father's name had not been taken away in all these years after his death. Dr. Pudor became city physician, holding the appointment for two years. In the meantime he had decided to go into the special field of dermatology, and in order to prepare himself fully he again went to Europe for study. He was greatly appreciated at the clinics in which he worked

and received several offers to stay, but he declined. While in Germany he married Fraulein Margarete Besig, but as he wished first to become established in the then new field of dermatology, he returned to America alone, leaving his young bride to follow him later. His new work gradually started and succeeded. He was house doctor for a few years at the Maine School for the Deaf, and then was elected to the new chair of dermatology at the Bowdoin Medical School, an appointment he held until this department of Bowdoin College was closed for lack of funds. He gained the love and admiration of his students both for his excellent teaching and human and humorous approach.

During the first World War he served as Captain in the United States Army at a Base Hospital at Camp Devens, Massachusetts.

Dr. Pudor was on the staff of the Maine General and Children's Hospitals until retired for age. The Venereal Disease Clinic of the Portland Dispensary was his special pet, and he devoted long years of intense work to it. In January, 1941, he suffered a second attack of influenza, which forced his retirement from practice, and he never regained full strength again. He had been a Fellow of the American College of Physicians since 1927, and during his active years thereafter he seldom missed any of its Annual Sessions.

Dr. Pudor was more than a dermatologist. He was a lovable human being. To a remarkable degree he always displayed that old-fashioned courtesy which makes one shrink from ever uttering a word that might wound the feelings of a brother practitioner. He was a modest man who carried his honors lightly; an honest man who spoke candidly; a friendly man who really was interested in his neighbors, his associates, and his patients; a truly Christian gentleman, who without professing any particular piety, exemplified in his daily life his faith and convictions that "it is better to give than to receive." To quote Osler, Dr. Pudor brought to the practice of medicine "the philosophy of hard work, the philosophy which insists that we are here, not to get all we can out of the life about us, but to see how much we can add to it."

For years I roomed with him as together we attended sessions of the American College of Physicians where, among a host of friends and acquaintances he was affectionately addressed as "Gus." Wherever we appeared there soon developed, through his charm of manner, his sincere cordiality, a camaraderie that was good to behold. Here was a nature "sloping toward the southern side," as Lowell put it, which made and kept friends. Early in life he learned that "temporal salvation depends on good food, abundant rest and cheerfulness." That he had attained in full measure. Ere this he must have heard the words, "good and faithful servant."

Selected from an Obituary in the
Journal of the Maine Medical Association
by E. W. GEHRING, M.D., F.A.C.P.,
former Governor for Maine